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{**Translator's note**: the items occurring on the last page have been moved here for the sake of continuity}

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[continued on back page]

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(54) **[Title of Invention] Drug with Active Ingredient of Dipeptide Compound with AHPBA Structure**

(57) **[Abstract]**
[Problem to be Solved] The object of the present invention is to provide a drug which has an outstanding HIV protease inhibition action which is useful as an HIV infection preventive agent or as an HIV infection therapeutic agent.
[Means Used to Resolve the Problem] A drug whose active ingredient is a compound represented by the following general formula:
[Formula 1]

{**Translator's note**: please see original document, first page}

[in the formula, R^1 is a displaceable aryl or heteroaryl (selected from α-group below); R^2 is an alkyl, a cycloalkyl, a hydroxy alkyl or a displaceable aralkyl (selected from β-group below) .
[α-group] C1-4 alkyl, OH, C1-4 alkoxy, C1-4 alkyl thio, halogen, trifluoromethyl, formyl, nitro and amino].
[β-group] C1-4 alkyl, C1-4 alkoxy and halogen.

Specification

[Scope of Patent Claim]
[Claim 1] A drug whose active ingredient is a compound indicated in brackets below.
General Formula
[Formula 1]

{**Translator's note** please see page 2 of original document, top of left-hand column}

[in the formula, R^1 is an aryl group or a heteroaryl group which may have a displacement group selected from α-group indicated below; R^2 is an alkyl group with a carbon number ranging from 1 to 6, a cycloalkyl group with a carbon number ranging from 3 to 8, a hydroxy alkyl group with a carbon number ranging from 1 to 6 or an aralkyl group which may have a displacement group selected from β-group indicated below;

[α-group] an alkyl group with a carbon number ranging from 1 to 4; a hydroxide group; an alkoxy group with a carbon number ranging from 1 to 4; an alkyl thio group with a carbon number ranging from 1 to 4; halogen atoms; a trifluoro methyl group; a formyl group, a nitro group and an amino group;

[β-group] an alkyl group with a carbon number ranging from 1to 4; an alkoxy group with a carbon number ranging from 1 to 4; halogen atoms;

[Claim 2] A drug whose active ingredient is a compound indicated as follows.
General Formula
[Formula 2]

{**Translator's note:** please see page 2 of original document, middle of left-hand column}

[in the formula, R^1 is an aryl group or a heteroaryl group which may have a displacement group selected from α-group as follows]

[α-group] an alkyl group with a carbon number ranging from 1 to 4; a hydroxide group; an alkoxy group with a carbon number ranging from 1 to 4; halogen atoms; a trifluoro methyl group; a formyl group, a nitro group and an amino group;

[Claim 3] The composition of Claim 1 wherein R^1 is a hydroxy phenyl group which has been displaced using a methyl, ethyl or propyl group;

[Claim 4] The composition of Claim1wherein R^1 is a 2-methyl phenyl, 3-hydroxy phenyl, 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl, 3-hydroxy-2-propyl phenyl, 3-methoxy-2-methyl phenyl, 3-fluoro-2-methyl phenyl or quinoline-4-yl group;

[Claim 5] The composition of Claim 1 wherein R^1 is a 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl or 3-hydroxy-2-propyl phenyl group;

[Claim 6] The composition of Claim 1 wherein R^2 is an n-butyl, tert-butyl, tert-pentyl, cyclo propyl, cyclo butyl or benzyl group;

[Claim 7] A drug whose active ingredient is a compound selected from the following: 3-(2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(3-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(4-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(3-methoxy-2-methyl benzoyl] amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(3-fluoro-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(2-ethyl-3-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline benzyl amide; 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline butyl amide; 3-(3-hydroxy-2-propyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(3-hydroxy-2-chlorobenzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide; 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline 4-fluorobenzyl amide;

[Claim 8] An HIV infection preventive agent which is made up of the compound mentioned in Claim 1 through Claim 7 and a carrier or excipient which is pharmacologically permissible;

[Claim 9] An HIV infection therapeutic agent which is made up of the compound mentioned in Claim 1 through Claim 7 and a carrier or excipient which is pharmacologically permissible;

[Claim 10] An AIDS preventive agent which is made up of the compound mentioned in Claim 1 through Claim 7 and a carrier or excipient which is pharmacologically permissible;

[Claim 11] An AIDS therapeutic agent which is made up of the compound mentioned in Claim 1 through Claim 7 and a carrier or excipient which is pharmacologically permissible;

[Claim 12] An HIV protease inhibitor which is made up of the compound mentioned in Claim 1 through Claim 7 and a carrier or excipient which is pharmacologically permissible;

[Detailed Description of Invention]
[0001]
[Industrial Field to Which Invention Belongs] The present invention relates to a drug which has an outstanding inhibition activity vis-a-vis protease originating in viruses occurring in acquired immune deficiency syndrome (HIV) (hereinafter, HIV protease) and whose active

ingredient is a new depeptide compound with an AHPBA (3-amino-2-hydroxy-4-phenyl butanate) structure.

[0002]
[Description of the Prior Art] AIDS is a disease which is caused by a retrovirus known as HIV which is one of the Lentiviriae. According to the World Health Organization (WHO), approximately 100 million persons throughout the world are currently suffering from this disease and the number of infected persons continues to grow. This disease is fatal and there is currently no effective therapy which can cure it.

[0003] The general characteristic of retrovirus replication is that it produces the maturation protein needed for the structure and function of viruses whereby the protease which produces the virus processes the precursor protein for the viruses. As a result, it is thought that if this processing is inhibited, production of infectious viruses can be prevented. For example, a paper by Kohl, N. E. et al. which appeared in **Proceedings of the National Academy of Sciences**, 85. 4686 (1988) makes it clear that infectious virions which have matured are not produced when the protease which is coded by the HIV become genetically inactive. In other words, it it thought that if the HIV protease is inhibited, it will be effective for prevention or treatment of HIV and for treatment of AIDS.

[0004] There have been proposals for an HIV protease inhibitor substance based on this concept and a great many inhibitor substances have been synthesized or are found in nature. There has been a report on exhibition of anti-HIV activity *in vitro* (Lang M., Rosel, **Journal of the Archives of Pharmacology**, 326, 921 (1993); Martin, J. A., **Antiviral Ros**, 17, 265 (1992); Meek, T.D., **Journal of Enzyme Inhibition**, 6, 65 (1992); [Japanese] Patent Number 5-222020; and **Journal of Medical Chemistry**, 36, 292 (1993).

[0005]
[Problem Which the Present Invention Attempts to Resolve] Despite this, substances which have been generally available have not been able to maintain for long periods of time a sufficient concentration of the drug in the blood needed to inhibit replication of HIV in infected cells in the body even when HIV protease inhibitors were administered orally or non-orally, which makes them impractical for clinical use.

[0006]
[Means Used to Resolve This Problem] The present invention contains dipeptide equivalents which have been sliced from HIV protease which are specific to HIV protease and which have outstanding inhibition activity and which are effective in cell tests even at low concentrations. The present invention also provides a low molecular HIV protease inhibitor which can obtain by oral or non-oral administration concentrations in the blood in which the HIV inhibition activity is sufficient *in vivo* which are calculated based on the effective concentration in cell tests.

[0007] The present invention is a drug whose active ingredient is a new dipeptide with an AHPBA structure which is represented by the following general formula.

[0008]
[Formula 3]

{**Translator's note**: please see page 3 of original document, upper right-hand column}

[0009] [in the formula, R^1 indicates an aryl group or a heteroaryl group which may have a displacement group which is selected from α-group indicated as follows; R^2 is an alkyl group with a carbon number ranging from 1 to 6, a cycloalkyl group with a carbon number ranging from 3 to 8, a hydroxy alkyl group with a carbon number ranging from 1 to 6, an aryl group which may have a displacement group selected from β-group indicated as follows or an aralkyl group which may have a displacement group selected from β-group indicated as follows.

[0010] [α-group]: an alkyl group with a carbon number ranging from 1 to 4; a hydroxide group; an alkoxy group with a carbon number ranging from 1 to 4; an alkyl thio group with a carbon number ranging from 1 to 4; halogen atoms; a trifluoromethyl group; a formyl group; a nitro group and an amino group.

[0011] [β-group]: an alkyl group with a carbon number ranging from 1 to 4; an alkoxy group with a carbon number ranging from 1 to 4; and halogen atoms.

[0012] The present invention is an HIV infection preventive agent, an HIV infection therapeutic agent, an AIDS preventive agent, an AIDS therapeutic agent and an HIV protease inhibitor which is made up of a compound indicated in general formula (I) above and a carrier or excipient which is pharmacologically permissible.

[0013] All of the following may be used as the "aryl group" in the "aryl group which may have a displacement group selected from α-group indicated as follows" for R^1: phenyl, 1-naphthyl and 2-naphthyl groups, with the phenyl group being especially suitable.

[0014] All of the following are suitable as the "heteroaryl group" in the "heteroaryl group which may have a displacement group selected from α-group as follows": thienyl, furyl, pyridyl, imidazolyl, quinolyl, isoquinolyl, indolyl, benzofuryl, naphthylidyl, quinoxalinyl, indazolyl, pyrolyl and pyrazinyl groups [all phonetically transcribed]; the most suitable being: pyridyl, quinolyl, isoquinolyl, indolyl, benzofuryl, naphthylidyl and quinoxalinyl groups.

[0015] All of the following are suitable as the alkyl group with carbon number ranging from 1 to 4 in α-group: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl and t-butyl groups; with the most suitable being the methyl and ethyl groups.

[0016] All of the following are suitable as the alkoxy group with carbon number ranging from 1 to 4 in α-group: methoxy, ethoxy, propyl oxy, isopropyl oxy, butyl oxy, isobutyl oxy, s-butyl oxy and t-butyl oxy group; with the methoxy group being especially suitable.

[0017] All of the following are suitable as the alkyl thio group with carbon number ranging from 1 to 4 in α-group: methyl thio, ethyl thio, propyl thio, isopropyl thio, butyl thio, isobutyl thio, s-butyl thio, t-butyl thio groups; with the methyl thio group being especially suitable.

[0018] All of the following may be used as the halogen atoms in α-group: fluorine, chlorine, bromine and iodine atoms; with fluorine and chlorine being especially suitable.

[0019] In addition to the "displacement groups which are selected from α-group indicated below" for the "aryl group which may have a displacement group selected from α-group indicated below", methyl, ethyl, propyl and hydroxide groups are especially suitable.

[0020] All of the following are generally suitable as the "aryl group which may have a displacement group selected from α-group indicated below" for R^1: 2-methyl phenyl, 3-hydroxy phenyl, 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl, 3-hydroxy-2-propyl phenyl, 3-methoxy-2-methyl phenyl, 3-fluoro-2-methyl phenyl groups; with the most suitable being: 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl, 3-hydroxy-2-propyl phenyl groups.

[0021] All of the following may generally be used as the "heteroaryl group which may have a displacement group selected from α-group as follows: 2-methyl pyridine-3-yl, quinoline-2-yl, isoquinoline-3-yl, indole-2-yl, 1-methyl indole-2-yl, benzofurane-2-yl, 2-methyl-1,8-naphthylidine-3-yl, 2-methyl-1,6-naphthylidine-3-yl, quinoxaline-2-yl and quinoline-4-yl groups, with the quinoline-4-yl group being especially suitable.

[0022] All of the following may be used as the "alkyl group with a carbon number ranging from 1 to 6" for R^2: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, tert-butyl, n-pentyl, isopentyl (tert-pentyl), 2-methyl butyl, neopentyl, 1-ethyl propyl, n-hexyl, isohexyl, 4-methyl pentyl, 3-methyl pentyl, 2-methyl pentyl, 1-methyl pentyl, 3,3-dimethyl butyl, 2,2-dimethyl butyl, 1,1-dimethyl butyl, 1,2-dimethyl butyl, 1,3-dimethyl butyl, 2,3-dimethyl butyl and 2-ethyl butyl groups; with the n-butyl, tert-butyl and tert-pentyl groups being especially suitable.

[0023] The "cycloalkyl group with a carbon number ranging from 3 to 8" for R^2 may be any of the following: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl groups with the cyclopropyl group and the cyclobutyl group being especially suitable.

[0024] By "hydroxy alkyl group with a carbon number ranging from 1 to 6" for R^2 is meant an "alkyl group with a carbon number ranging from 1 to 6" as previously indicated which has been displaced using a hydroxide group. The following are all suitable for this: hydroxy methyl, 1-hydroxy ethyl, 2-hydroxy ethyl and 3-hydroxy propyl groups.

[0025] Any of the following may be used as the "aryl group" for the "aryl group which may have a displacement group selected from β-group indicated as follows" for R^2: phenyl, 1-naphthyl and 2-naphthyl groups, with the phenyl group being especially suitable.

[0026] Any of the following may be used as the "aralkyl group" for the "aralkyl group which may have a displacement group selected from β-group indicated as follows" for R^2: benzyl and phenethyl groups, with the benzyl group being especially suitable.

[0027] Any of the following may be used as the "alkyl group with a carbon number ranging from 1 to 4" in β-group: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl and t-butyl groups, with the methyl, ethyl and propyl groups being especially suitable.

[0028] Any of the following may be used as the "alkoxy group with a carbon number ranging from 1 to 4" in β-group: methoxy, ethoxy, propyl oxy, isopropyl oxy, butyl oxy, isobutyl oxy, s-butyl oxy and t-butyl oxy groups, with the methoxy group being especially suitable. Any of the following may be used as the "halogen atoms" in β-group: fluorine, chlorine, bromine and iodine, with fluorine and chlorine being especially suitable.

[0029] A non-displaced phenyl group is the most suitable "aryl group which may have a displacement group selected from β-group indicated as follows" for R^2.

[0030] Any of the following may be used as the "aralkyl group which may have a displacement group selected from β-group indicated as follows" for R^2: benzyl, 4-methoxy benzyl, 4-fluorobenzyl and 3-methyl benzyl groups, with the benzyl group being especially suitable.

[0031] All of the following are suitable for R^1: 2-methyl phenyl, 3-hydroxy phenyl, 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl, 3-hydroxy-2-propyl phenyl, 3-methoxy-2-methyl phenyl, 3-fluoro-2-methyl phenyl and quinoline-4-yl groups. 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl and 3-hydroxy-2-propyl phenyl groups are especially suitable.

[0032] The following are all suitable for R^2: n-butyl, tert-butyl, tert-pentyl, cyclopropyl, cyclobutyl or benzyl groups.

[0033] The following compounds in the present invention are suitable.

2) Compounds in which R^2 is a tert butyl group;
3) Compounds in which R^1 is a hydroxy phenyl group displaced by a methyl, ethyl or propyl group;
4) Compounds in which R^1 is a 2-methyl phenyl, 3-hydroxy phenyl, 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl, 3-hydroxy-2-propyl phenyl, 3-methoxy-2-methyl phenyl, 3-fluoro-2-methyl phenyl or quinoline-4-yl group.
5) Compounds in which R^1 is a 3-hydroxy-2-methyl phenyl, 3-hydroxy-2-ethyl phenyl or a 3-hydroxy-2-propyl phenyl group.
6) Compounds in which R^2 is a butyl, tert-butyl, tert-pentyl, cyclopropyl, cyclobutyl or a benzyl group.

[0034] Compound (1) in the present invention has asymmetric carbon [atoms] inside the molecules and although stereoisomers which are R and S configurations are present in each of these, each of these or mixtures of them are included in the present invention.

[0035] When compound (1) in the present invention is set out in the atmosphere, it may absorb moisture, hydroscopic water may become attached to it and it may become a hydrate. This type of salt is also included in the present invention.

[0036] Although representative compounds in the present invention are indicated in Table 1 as follows, it should by no means be construed that the compound in the present invention is restricted to these.

[0037]
[Formula 4]

{**Translator's note**: please see page 5 of original document, upper right-hand column}

[0038]
[Table 1]

Illustration Number	R^1	R^2
1	phenyl	tert-butyl
2	2-methyl phenyl	tert-butyl
3	2-hydroxy phenyl	tert-butyl
4	2-methoxy phenyl	tert-butyl
5	2-fluoro phenyl	tert-butyl
6	2-trifluoro methyl phenyl	tert- butyl
7	3-methyl phenyl	tert- butyl
8	3-hydroxy phenyl	tert- butyl
9	3-methoxy phenyl	tert- butyl
10	3-fluoro phenyl	tert- butyl
11	4-methyl phenyl	tert- butyl
12	4-hydroxy phenyl	tert- butyl
13	4-methoxy phenyl	tert- butyl
14	4-fluoro phenyl	tert- butyl
15	3-hydroxy-2-methyl phenyl	tert- butyl
16	3-methoxy-2-methyl phenyl	tert- butyl
17	2-hydroxy-3-methoxy phenyl	tert- butyl
18	3-fluoro-2-methyl phenyl	tert- butyl
19	2,3-difluoro phenyl	tert- butyl
20	3-hydroxy-4-methoxy phenyl	tert- butyl
21	2-bromo-3-hydroxy phenyl	tert- butyl
22	3-formyl phenyl	tert- butyl
23	2-ethyl-3-hydroxy phenyl	tert- butyl
24	3,5-difluoro phenyl	tert- butyl
25	3,5-dihydroxy phenyl	tert- butyl
26	2-methyl-3-nitro phenyl	tert- butyl
27	3-thionyl	tert- butyl
28	3-furyl	tert- butyl
29	2-hydroxy pyridine-3-yl	tert- butyl
30	3-hydroxy pyridine-2-yl	tert- butyl

31	2,5-hydroxy pyridine-4-yl	tert- butyl
32	2-methyl pyridine-3-yl	tert- butyl
33	3-hydroxy-4-methyl phenyl	tert- butyl
34	3,5-hydroxy-2-methyl phenyl	tert- butyl
35	2-isopropyl-3-hydroxy phenyl	tert- butyl
36	2-thienyl	tert- butyl
37	3-furyl	tert- butyl
38	4-methyl imidazole-5-yl	tert- butyl
39	pyridine-2-yl	tert- butyl
40	pyridine-3-yl	tert- butyl
41	pyridine-4-yl	tert- butyl
42	4-bromopyridine-3-yl	tert- butyl
43	5-chloropyridine-3-yl	tert- butyl
44	6-methyl pyridine-3-yl	tert- butyl
45	2,6-dichloropyridine-3-yl	tert- butyl
46	5,6-dichloropyridine-3-yl	tert- butyl
47	2-chloro-6-methyl pyridine-3-yl	tert- butyl
48	2-hydroxy-6-methyl pyridine-3-yl	tert- butyl
49	5-chloro-6-hydroxy pyridine-3-yl	tert- butyl
50	1-naphthyl	tert- butyl
51	2-naphthyl	tert- butyl
52	1-hydroxy-1-naphthyl	tert- butyl
53	1-hydroxy-2-naphthyl	tert- butyl
54	3-hydroxy-2-naphthyl	tert- butyl
55	4-fluoro-1-naphthyl	tert- butyl
56	3,5-dihydroxy-2-naphthyl	tert- butyl
57	3,7-dihydroxy-2-naphthyl	tert- butyl
58	quinoxaline-2-yl	tert- butyl
59	3-hydroxy quinoxaline-2-yl	tert- butyl
60	quinoline-2-yl	tert- butyl
61	quinoline-3-yl	tert- butyl
62	quinoline-4-yl	tert- butyl
63	quinoline-8-yl	tert- butyl
64	4-hydroxy quinoline-2-yl	tert- butyl
65	4-methoxy quinoline-2-yl	tert- butyl
66	4,8-dihydroxy quinoline-2-yl	tert- butyl
67	isoquinoline-1-yl	tert- butyl
68	isoquinoline-3-yl	tert- butyl
69	isoquinoline-8-yl	tert- butyl
70	indole-2-yl	tert- butyl
71	indole-3-yl	tert- butyl
72	indole-4-yl	tert- butyl
73	indole-5-yl	tert- butyl
74	1-methyl indole-2-yl	tert- butyl
75	5-fluoro indole-2-yl	tert- butyl
76	5-chloro indole-2-yl	tert- butyl

77	5-hydroxy indole-2-yl	tert- butyl
78	5-methoxy indole-2-yl	tert- butyl
79	4-methoxy indole-2-yl	tert- butyl
80	6-methoxy indole-2-yl	tert- butyl
81	benzofurane-2-yl	tert- butyl
82	7-methoxy benzofurane-2-yl	tert- butyl
83	1,8-naphthylidine-2-yl	tert- butyl
84	1,6-naphthylidine-2-yl	tert- butyl
85	2-methyl-1, 8-naphthylidine-3-yl	tert- butyl
86	2-trifluoro methyl-1,8-naphthylidine-3-yl	tert- butyl
87	2-methyl-1,6-naphthylidine-3-yl	tert- butyl
88	2-trifluoro methyl-1,6-naphthylidine-3-yl	tert- butyl
89	1-methyl indazole-3-yl	tert- butyl
90	3-hydroxy pyratine-2-yl	tert- butyl
91	pyrrole-2-yl	tert- butyl
92	1-methyl pyrrole-2-yl	tert- butyl
93	3-hydroxy-2-methyl phenyl	benzyl
94	3-hydroxy-2-methyl phenyl	butyl
95	2-chloro-5-methyl thiophenyl	tert- butyl
96	2-methyl-3-benzyl oxycarbonyl aminophenyl	tert- butyl
97	3-amino-2-methyl phenyl	tert- butyl
98	1-iodophenyl	tert- butyl
99	3-hydroxy-2-propyl phenyl	tert- butyl
100	2-methyl-naphthalene-1-yl	tert- butyl
101	2-chloro phenyl	tert- butyl
102	acridine-3-yl	tert- butyl
103	2-ethyl phenyl	tert- butyl
104	2-bromophenyl	tert- butyl
105	2,3-dimethyl phenyl	tert- butyl
106	anthracene-9-yl	tert- butyl
107	3-propionyl oxy-2-methyl phenyl	tert- butyl
108	3-hydroxy-2-methyl phenyl	tert- pentyl
109	5-hydroxy pyridine-2-yl	tert- butyl
110	3-hydroxy-2-methyl phenyl	1,1-dimethyl-2-hydroxy ethyl phenyl
111	3-hydroxy-2-methyl phenyl	phenyl
112	3-hydroxy-2-methyl phenyl	4-fluorobenzyl
113	2-methyl phenyl	methyl
114	3-hydroxy phenyl	methyl
115	4-hydroxy phenyl	methyl
116	3-hydroxy-2-methyl phenyl	methyl
117	3-methoxy-2-methyl phenyl	methyl
118	3-fluoro-2-methyl phenyl	methyl
119	2-ethyl-3-hydroxy phenyl	methyl
120	3-hydroxy-2-propyl phenyl	methyl
121	2-chloro phenyl	methyl

122	2-methyl phenyl	ethyl
123	3-methyl phenyl	ethyl
124	4-hydroxy phenyl	ethyl
125	3-hydroxy-2-methyl phenyl	ethyl
126	3-methoxy-2-methyl phenyl	ethyl
127	3-fluoro-2-methyl phenyl	ethyl
128	2-ethyl-3-hydroxy phenyl	ethyl
129	3-hydroxy-2-propyl phenyl	ethyl
130	2-chloro phenyl	ethyl
131	2-methyl phenyl	propyl
132	3-hydroxy phenyl	propyl
133	4-hydroxy phenyl	propyl
134	3-hydroxy-2-methyl phenyl	propyl
135	3-methoxy-2-methyl phenyl	isopropyl
136	3-fluoro-2-methyl phenyl	isopropyl
137	2-ethyl-3-hydroxy phenyl	isopropyl
138	3-hydroxy-2-propyl phenyl	isopropyl
139	2-chloro phenyl	isopropyl
140	2-methyl phenyl	pentyl
141	3-hydro phenyl	pentyl
142	4-hydroxy phenyl	pentyl
143	3-hydroxy-2-methyl phenyl	pentyl
144	3-methoxy-2-methyl phenyl	pentyl
145	3-fluoro-2-methyl phenyl	pentyl
146	2-ethyl-3-hydroxy phenyl	hexyl
147	3-hydroxy-2-methyl phenyl	hexyl
148	3-hydroxy-2-propyl phenyl	hexyl
149	2-chloro phenyl	hexyl
150	2-methyl phenyl	cyclopropyl
151	3-hydroxy phenyl	cyclopropyl
152	4-hydroxy phenyl	cyclopropyl
153	3-hydroxy-2-methyl phenyl	cyclopropyl
154	3-methoxy-2-methyl phenyl	cyclopropyl
155	3-fluoro-2-methyl phenyl	cyclopropyl
156	2-ethyl-3-hydroxy phenyl	cyclopropyl
157	3-hydroxy-2-propyl phenyl	cyclopropyl
158	2-chloro-phenyl	cyclopropyl
159	2-methyl phenyl	cyclobutyl
160	3-hydroxy phenyl	cyclobutyl
161	4-hydroxy phenyl	cyclobutyl
162	3-hydroxy-2-methyl phenyl	cyclobutyl
163	3-methoxy-2-methyl phenyl	cyclobutyl
164	3-fluoro-2-methyl phenyl	cyclobutyl
165	2-ethyl-3-hydroxy phenyl	cyclobutyl
166	3-hydroxy-2-propyl phenyl	cyclobutyl
167	2-chloro phenyl	cyclobutyl

168	2-methyl phenyl	cyclopentyl
169	3-hydroxy phenyl	cyclopentyl
170	4-hydroxy phenyl	cyclopentyl
171	3-hydroxy-2-methyl phenyl	cyclopentyl
172	3-methoxy-2-methyl phenyl	cyclopentyl
173	3-fluoro-2-methyl phenyl	cyclopentyl
174	2-ethyl-3-hydroxy phenyl	cyclopentyl
175	3-hydroxy-2-propyl phenyl	cyclohexyl
176	2-chloro phenyl	cyclohexyl
177	2-methyl phenyl	cycloheptyl
178	3-hydroxy phenyl	cycloheptyl
179	4-hydroxy phenyl	cycloheptyl
180	3-hydroxy-2-methyl phenyl	cycloheptyl
181	3-methoxy-2-methyl phenyl	cycloheptyl
182	3-fluoro-2-methyl phenyl	cycloheptyl
183	2-ethyl-3-hydroxy phenyl	cyclooctyl
184	3-hydroxy-2-propyl phenyl	cyclooctyl
185	2-chloro phenyl	cyclooctyl
186	3-hydroxy-2-methyl phenyl	cyclooctyl
187	2, 6-dimethyl phenyl	tert- butyl
188	2-methyl phenyl	phenyl
189	3-hydroxy phenyl	phenyl
190	4-hydroxy phenyl	phenyl
191	3-methoxy-2-methyl phenyl	phenyl
192	3-fluoro-2-methyl phenyl	phenyl
193	2-ethyl-3-hydroxy phenyl	phenyl
194	3-hydroxy-2-propyl phenyl	phenyl
195	2-chloro phenyl	phenyl

In the Table above, suitable compounds are as follows: 3-(2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide **(Illustrative Compound Number 2)**; 3-(3-hydroxy-benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-1, -proline tert-butyl amide **(Illustrative Compound Number 8)**; 3-(4-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide **(Illustrative Compound Number 12)**; 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide **(Illustrative Compound Number 15)**; 3-(3-methoxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide **(Illustrative Compound Number 16)**; 3-(3-fluoro-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide **(Illustrative Compound Number 18)**; 3-(2-ethyl-3-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline tert-butyl amide **(Illustrative Compound Number 23)**; 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline benzyl amide **(Illustrative Compound Number 93)**; 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline butyl amide **(Illustrative Compound Number 99)**; 3-(3-hydroxy-2-chlorobenzoyl) amino-2-hydroxy-4-phenyl benzoyl) amino-2-hydroxy-4-phenyl benzoyl-4-chlor-L-proline tert-butyl

amide **(Illustrative Compound Number 101)**; and 3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4-chlor-L-proline 4-fluorobenzyl amide **(Illustrative Compound Number 112)**.

[0039]
[Practical Configuration of the Invention]
Next, we shall describe the method of manufacturing the compound which is an active ingredient in the drug in the present invention.

[0040]
[Formula 3]

{**Translator's note**: please see page 10 of original document}

[0041] In the above-mentioned formula, R^1 and R^2 indicate the same as they did previously. R^3 and R^4 are the same and indicate an aryl methyl base which may be displaced by a lower alkyl, a lower alkoxy or a hydroxide base; or a hydrogen atom. On the other hand, it may indicate a protective group for an amino group other than an aryl methyl group.

[0042] In addition to the aryl methyl group which may be displaced using a lower alkyl, a lower alkoxy or a hydroxyl group for R^3 and R^4, a benzyl, 4-methyl benzyl, 4-methoxy benzyl, 4 ethyl benzyl, 4-ethoxy benzyl and 4-hydroxy benzyl group may also be used.

[0043] As long as any commonly used "protective group for the amino group other than an aryl methyl group" is used for R^3 and R^4, there are no restrictions. However, the following are all suitable as the aforementioned "aliphatic acyl group": benzoyl, aryl carbonyl groups such as α-naphthoyl, β-naphthoyl, halogenated aryl carbonyl groups such as 2-bromobenzoyl and 4-chlorobenzoyl, lower alkylated carbonyl groups such as 2,4,6- trimethyl benzoyl and 4-toluoyl, lower alkoxylated aryl carbonyl groups such as 4-anisoyl, nitrated aryl carbonyl groups such as 4-nitrobenzoyl and 2-nitrobenzoyl, lower alkoxy carbonyl groups such as 2-(methoxy carbonyl) benzoyl, arylated aryl carbonyl groups such as 4-phenyl benzoyl and other aromatic acyl groups; lower alkoxy carbonyl groups such as methoxy carbonyl, ethoxy carbonyl, t-butoxy carbonyl and isobutoxy carbonyl, lower alkoxy carbonyl groups and other alkoxy carbonyl groups which have been displaced by halogenated or lower alkyl ethoxy carbonyl groups such as 2,2,2-trichloro ethoxy carbonyl and 2-trimethyl silyl [phonetic] ethoxy carbonyl; alkenyl oxycarbonyl groups such as vinyl carbonyl and allyl oxycarbonyl; aralkyl oxy carbonyl groups whose aryl ring may be displaced by one or two lower alkoxy or nitro groups such as benzyl oxycarbonyl, 4-methoxy benzyl oxy carbonyl, 3,4-dimethoxy benzyl oxycarbonyl, 2-nitrobenzyl oxy carbonyl, 4-nitrobenzyl oxycarbonyl; trilower alkoxy silyl [phonetic] groups such as trimethyl silyl [phonetic], triethyl cyllyl, isopropyl dimethyl silyl [phonetic], t-butyl dimethyl silyl [phonetic], methyl diisopropyl silyl [phonetic] and methyl di-t-butyl silyl [phonetic], triisopropyl silyl [phonetic], lower alkyl silyl [phonetic] groups and other silyl [phonetic] groups which may be displaced by one or two aryl groups such as disphenyl methyl silyl [phonetic], diphenyl butyl silyl [phonetic] and phenyl diisopropyl silyl [phonetic].

[0044] The compound (III) used as the starting substance may be any already known substance or may be synthesized using an already known method. The 4-chloro proline in compound (III) may be made using the method which is based on hydrochloric acid using 4-hydroxy proline, a method which uses phosphorus trichloride, a method which uses thionyl chloride or phosphorus oxychloride or other halides. The most suitable are the method which uses N-chlorosuccinate imide according to the method used by A.K. Bose and others in **Tetrahedron Letters,** 40, 3937 (1973); or the method which uses carbon tetrachloride and triphenyl phosphein according to J.G. Calzada S(Org. Syn., 6, 634). Compound (II) which is used as a starting substance may be a substance which is already known or may be easily synthesized using an already known method. It may be synthesized, for example, using the method used by R. Horanz and others (**Synthesis,** 703 (1989) and the method used by M. T. Reets and others (**Tetrahedron Letters.**, 29, 3295 (1988).

[0045] The compound (III) used as the starting substance may be any one which is already known or it may be synthesized using an already known method. It may be manufactured by chlorinating the hydroxide group of N-(tert- butoxy carbonyl)-3-hydroxy proline, then, amidating the carboxylic acid, then removing the tert-butoxy carbonyl group which is a protective group or by first amidating the carboxylic acid, then chlorinating the hydroxide group and then removing the tert-butoxy carbonyl group which is a protective group.

[0046] We shall explain in detail the processes for each of the above-mentioned methods which are examples of manufacturing the compound in the present invention.

[0047] The first step is the process which is used to manufacture compound (II) or a carboxylic acid reactive derivative of it and compound (IV) by reacting an amino compound (III).

[0048] As long as it is based on the standard peptide synthesis method, the reaction can be carried out by using the azide method, the activated esterification method, the mixed acid anhydride method or the condensation method.

[0049] The azide method involves reacting an amino acid hydrazine--which is manufactured by reacting an amino acid or an ester of it in an inert solvent near room temperature—with a nitrite compound, then substituting it for the azide compound, then processing it as an amine compound.

[0050] The nitride compound used may be an alkali metal nitrite such as sodium nitrite or a nitrite alkyl compound such as isoamyl nitrite.

[0051] The inert solvent used here may be an amide such as dimethyl formamide or dimethyl acetoamide; or a pyrrolidone such as N-methyl pyrrolidone.

[0052] The two reactions in this process are normally carried out in a single reaction solution. The reaction temperature should be – 50 to 0°C in the previous stage and –10 to 10°C in the latter stage. The reaction time should range from 5 minutes to one hour for the previous stage and from 10 hours to five days for the latter stage.

[0053] The activated esterification method is carried out by reacting an activated esterification agent in a solvent with an amino acid, manufacturing an activated ester and then reacting it with an amine compound.

[0054] As long as the solvent used is activated, any of the following may be used for the activated solvent: methylene chloride, chloroform and other halogenated hydrogen carbides; ether, tetrahydrofurane and other ethers; dimethyl formamide, demethyl acetoamide and other amides.

[0055] Any of the following may be used as the activated esterification agent: N-hydroxy succiimide, 1-hydroxybenzotriazole, N-hydroxy-5-norbornene [phonetic]-2, 3-dicarboxyimide and other N-hydroxy compounds. The activated esterification reaction should optimally be carried out in the presence of dicyclohexyl carbodiimide (DCC) and other condensation agents. Condensation may also be carried out in the presence of 1,1'-oxalyl diimidazole, 2,2'-dipyridyl disulfide, N,N'-disuccinimidyl carbonate, diphenyl phosphate azide (DPPA), diethyl cyanophosphate (DEPC) , N,N'-bis (2-oxo-3-oxazolidinyl) phosphenic chloride (BOP-C1), N, N'-carbonyl diimidazole), N,N'disuccinimidyloxalate (DSO), N,N'-diphthalimidoxalate (DPO), N,N'-bis (norbornenyl [phonetic] succinimidyl) oxalate (BNO), 1, 1'-bis (benzotriazolyl) oxalate (BBTO), 1,1'-bis (6-chlorobenzotriazolyl) oxalate (BCTO), 1,1'-bis (6-trifluoro methyl benzotriazolyl) oxalate (BTBO) and brom-tris-pyrrolidino-phosphonium-hexafluoro-phosphate (PyPrOP).

[0056] The reaction temperature should be 10 to 25° C in the activated esterification reaction and should be room temperature in the reaction of the activated esterification compound and the amines. The reaction time should be from 30 minutes to 10 hours for both reactions.

[0057] The mixed acid anhydride method is carried out by first manufacturing a mixed acid anhydride of the amino acid and then reacting it with the amines.

[0058] The reaction which is used to manufacture the mixed acid anhydride is carried out by reacting ethyl chlorocarbonate, isobutyl chlorocarbonate and other lower alkyl halide carbonates, diethyl cyanophosphate (DEPC) and other lower alkyl cyanophosphates or diphenyl phosphate azides (DPPA) and amino acid in an inert solvent (such as ether, tetrahydrofurane and other ethers, dimethyl formamide, dimethyl acetoamide and other amides).

[0059] The reaction should optimally be carried out in the presence of triethyl amine, N-methyl morpholine and other organic amines. The reaction temperature should be from –10 to 25°C and the reaction time should be from 30 minutes to five hours.

[0060] The reaction between the mixed acid anhydride and the amine should optimally be carried out in the presence of the aforementioned organic amine in an inert solvent (such as ether, tetrahydrofurane and other ethers; dimethyl formamide, dimethyl acetoamide and other amines). The reaction temperature should be from 0°C to room temperature and the reaction time should be from one hour to 24 hours.

[0061] The condensation method is carried out in the same way as the reaction used to manufacture the aforementioned inert ester by directly reacting the amino acid and the amine in the presence of dicyclohexyl carboxiimide, carbonyl diimidazole and other condensation agents.

[0062] The second step involves manufacturing compound (V) by removing the protective group of the amino group of compound (IV) using a solvent.

[0063] When a silyl [phonetic] group is used as a protective group for the amino group, it can usually be removed by processing using tetrabutyl ammonium fluoride, potassium fluoride and other fluorine anions.

[0064] There are no particular restrictions on the reaction solvent used as long as it does not inhibit the reaction, however, tetrahydrofurane, dioxane and other ethers are most suitable.

[0065] Although there are no particular restrictions on the reaction temperature, the reaction should be carried out at room temperature and between 10 to 18 hours.

[0066] When a t-butyl oxycarbonyl group such as an alkoxy carbonyl group is used as the protective group for the amino group, it can be removed by processing with an acid using an inert solvent.

[0067] There are no particular restrictions on the reaction solvent used as long as it does not inhibit the reaction and the following are all suitable: dimethyl formamide, dimethyl acetoamide and other amides; diethyl ether, diisopropyl ether, tetrahydrofurane, dioxane, dimethoxy ethane, diethylene glycol dimethyl ether and other ethers; methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, dicyclohexanol, methyl cellosolve and other alcohols; diclor methane, chloroform, trichlorethane and other halogenated hydrogen carbides.

[0068] There are no particular restrictions on the acid used as long as it is an acid. The following are the most suitable: hydrochloric acid and other anhydrides, trifluoro acetate and other organic acids, boron trifluoride ether complexes and other Lewis acids.

[0069] There are no particular restrictions on the reaction temperature and the reaction time, but these normally range from 0 to 30°C and from 20 minutes to one hour.

[0070] When the protective group of the amino group is a displaced methyl group which forms an aliphatic acyl group, an aromatic acyl group or a Schiff base, it can be removed by processing in the presence of an aqueous solvent using an acid or a base.

[0071] There are no particular restrictions on the acid used as long as it is an acid commonly used and the following are all suitable: hydrochloric acid, sulfuric acid, phosphoric acid, hydrogen bromide and other inorganic acids. There are no restrictions on the base used as long as it does not adversely affect the other functional groups in the compound and any of the following are suitable: sodium methoxide and other metal alkoxides, sodium carbonate, potassium carbonate and other alkali metal carbonates, sodium hydroxide, potassium hydroxide

and other alkali metal hydroxides or aqueous ammonia, concentrated ammonium methanol and other ammonia.

[0072] Isomerization sometimes occurs in hydrolysis using a base.

[0073] There are no particular restrictions on the solvent used as long as it is used in the normal hydrolytic reaction and water, methanol, ethanol, n-propanol and other alcohols, tetrahydrofurane, dioxane and other ethers and organic solvents or mixed solvents of water and the above-mentioned solvent are all suitable.

[0074] There are no particular restrictions on the reaction temperature and the reaction time since the starting substance and the base used are different. However, the reaction is normally carried out at a temperature ranging from 0 to 150°C and from one hour to ten hours in order to inhibit any side reaction.

[0075] When the protective group for the amino group is an aralkyl oxycarbonyl group, it can be removed by reducing in an inert solvent in the presence of a catalytic reduction catalyst.

[0076] There are no particular restrictions on the solvent used as long it is one which is normally used for reduction reactions and all of the following are suitable: diethyl ether, diisopropyl ether, tetrahydrofurane, dioxane, dimethoxy ethane, diethylene glycol dimethyl ether and other ethers; methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, [one letter illegible]-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol, methyl cellosolve and other alcohols.

[0077] Palladium carbon, palladium black and the like may be used as the catalytic reduction catalyst.

[0078] The reaction temperature and the reaction time are different depending on the starting substance and there are no particular restrictions on these. However, reaction time should normally range from one hour to eight hours with hydrogen pressure ranging from normal pressure to 10 atms near room temperature.

[0079] When the protective group for the amino group is an aryl methyl group, it can usually be removed by bringing it in contact with a reducing agent in a solvent. The most suitable method of removing it involves carrying out a catalytic reduction in a catalyst at ordinary temperature or by using a method which uses an oxidizing agent.

[0080] There are no particular restrictions on the solvent used for removal using catalytic reduction as long as it contributes to the main reaction and any of the following are suitable: methanol, ethanol, isopropanol and other alcohols; diethyl ether, tetrahydrafurane, dioxane and other ethers; toluene, benzene, xylene and other aromatic hydrogen carbides; hexane, cyclohexane and other aliphatic hydrogen carbides; ethyl acetate, propyl acetate and other esters; formic acid, acetic acid and other mixed solvents of fatty acids or mixtures of organic solvents of these and water or mixed solvents of fatty acids and alcohols.

[0081] There are no particular restrictions on the catalyst used as long as it is used for the catalytic reduction reaction and the following may be used: palladium black, palladium carbon, Raney nickel, platinum oxide, platinum black, rhodium-aluminum oxide, triphenyl phosphein-rhodium chloride and palladium-barium sulfate.

[0082] There are no particular restrictions on the pressure and it should normally be from one to 10 atm.

[0083] The reaction temperature and the reaction time differ depending on the starting substance and the type of catalyst, however these should usually be from 0 to 100°C and from five minutes to 24 hours.

[0084] There are no particular restrictions on the solvent used for removal by oxidation as long as it does not contribute to the main reaction, however, a water-containing organic solvent is particularly suitable.

[0085] This type of organic solvent should optimally be an acetone such as a ketone; methylene chloride, chloroform, carbon tetrachloride and other halogenated hydrogen chlorides; acetonitriles and other nitriles; diethyl ether, tetrahydofurane, dioxane and other ethers, dimethyl formamide, dimethyl acetoamide, hexamethyl phosphorotriamide and other amides and dimethyl sulfoxy and other sulfoxides.

[0086] There are no particular restrictions on the oxidizing agent used as long as it is a compound which is used for oxidation and all of the following are suitable: potassium persulfate, sodium persulfate, ammonium cerium nitrate (CAN) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ).

[0087] The reaction temperature and the reaction time differ depending on the starting substance and the type of catalyst, however, they should normally range from 0 to 150°C and from ten minutes to 24 hours.

[0088] When the protective group for the amino group is a diaryl methyl group, processing is carried out under the same conditions as the aforementioned aryl methyl group removal reaction.

[0089] When the protective group for the amino group is an alkenyl oxycarbonyl group, this can usually be carried out using a base under the same conditions and reducing reaction as when the protective group for the amino group is a displaced methylene group which forms the aforementioned aliphatic acyl group, aromatic acyl group, alkoxy carbonyl group or Schiff base.

[0090] When an allyl oxycarbonyl is used, it is easy to make the removal using palladium and triphenyl phosphein or nickel tetracarbonyl so that there is little side reaction.

[0091] The third step involves manufacturing compound (1I in the present invention by reacting compound (VI) or a reactive derivative of a carboxylic acid of it and compound (V) as was the case in the first step.

[0092] After the reaction in each of the aforementioned steps is completed, each of the target compounds is collected from the reactive mixture using the usual method. For example, they can be obtained by suitably neutralizing the reactive mixture or by first removing by filtering when insoluble matter is present and then adding an organic solvent which does not mix with water, then washing and removing the solvent. If necessary, it can be further purified by using the normal method, that is, recrystallization, resedimentation or chromatography and the like.

[0093] When reducing the present invention to practice, that is, when using compound (I) as an HIV infection preventive agent, an HIV therapeutic agent, an AIDS prevention agent, an AIDS therapeutic agent or an HIV protease inhibitor, it may be administered orally in pill form, in capsules, granules, powder or as a syrup and the like or by injection or non-orally as a suppository. These preparations are manufactured by using a well known method using (1) an excipient (such as lactose, saccharose, glucose, mannite, sorbit and other sugar derivatives; corn starch, potato starch, α starch, dextrin, carboxy methyl starch and other starch derivatives; crystal cellulose, low displacement hydroxy propyl cellulose, hydroxy propyl methyl cellulose, carboxy methyl cellulose, carboxy methyl cellulose calcium, internal bridging sodium carboxy methyl cellulose and other cellulose derivatives; gum arabic; dextrin; pullulan and other organic group excipients; and light silicic anhydrides; synthetic aluminum silicate; magnesium metasilicate aluminate and other silicate derivatives; calcium phosphate and other phosphates; calcium carbonate and other carbonates; calcium sulfate and other sulfates and other inorganic group excipients); **lubricants** (such as stearic acid, calcium stearate, magnesium stearate and other stearate metal salts; talc; colloid silica; beeswax, spermaceti and other waxes; boric acid; adipic acid; sodium sulfate and other sulfates; glycol; fumaric acid, sodium benzoate; DL leucin; fatty acid sodium salt; sodium lauryl sulfate; magnesium lauryl sulfate and other lauryl sulfates; silicic anhydrides; silicon hydrate and other silicates; and starch derivatives of these); **bonding agents** (for example, polyvinyl pyrrolidone, "macrogoles" [phonetic] and the same type of compounds as with the excipients indicated above); **disintegrators** (for example, the same type of compounds as for the excipients indicated above and sodium cross carmelose; sodium carboxy methyl statin, bridging polyvinyl pyrrolidone and other chemically modified starches / celluloses); **stabilizers** (methyl "parabene" [phonetic], propyl "parabene" and other paraoxy benzoate esters; chlorobutanol, benzyl alcohol, phenyl ethyl alcohol and other alcohols; "benzalconium" [phonetic] chloride; phenols, cresoles and other phenols; "cymerosale" [phonetic]; hydroacetate; and sorbic acid); **taste and odor modification agents** (such as sweeteners, tartness agents, perfumes and the like); **diluents** and other additives may be used. The amount used differs depending on the symptoms, age, method of administration and the like. However, when administering orally, a lower limit of 200 mg (and preferably 300 mg) and an upper limit of 1200 mg (and preferably 1000 mg) per time should be given when administering orally. A lower limit of 20 mg (and preferably 30 mg) and an upper limit of 120 mg (and preferably 100 mg) should be given one to several times per day depending on the symptoms when administering intravenously.

[0094]
[Practical Embodiments of the Invention]

[Practical Embodiment 1] (2S, 3S) – 3 – (3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-[number is illegible]-phenyl butanoyl-[4 (S)-chloro]-L-proline tert-butyl amide (Illustrative

Compound Number 15) We stirred at room temperature a tetrahydrofurane solution (25 ml) made up of 445 g (9.02 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chloro]-L-proline tert-butyl amide 3; 3.05 g (15.9 mmol) of 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride (hereinafter abbreviated to EDC); 510 g (9.92 mmol) of 3-hydroxy-2-methyl benzoate 1 (reference work: **Organic Preparation and Procedures Intl**. 1979, 11, 27); and 35 g (9.96 mmol) of 1-hydroxy benzotriazole (hereafter abbreviated to HOBt); and stirred it for six hours. We added an aqueous solution of saturated sodium hydrogencarbonate and stopped the reaction. We diluted this reactive mixed solution using methylene chloride. Then, we washed successively the organic layers using a saturated sodium hydrogencarbonate aqueous solution and saturated brine and dried it using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the residue obtained using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it and obtained 4.25 g (yield of 91 %) of the indicated compound as a colorless crystalline solid.

[0095] ^{1} H-NMR : δ ppm ($CDCl_3$, 270 MHz): 7.33-7.14 (m. 5H), 7.03-6.93 (m.1H), 6.84-6.17 (m.3H), 5.96 (s.3H), 5.94 (s.1H), 4.73-4.30 (m.4H), 4.18-3.48 (m,2H), 2.77-2.21 (m. 4H), 1.30 (s.9H).
IR (KBr): 3325, 2969, 2931, 1648, 1586, 1526, 1455, 1367, 1282, 1225, 1208, 1176, 1112, 1093, 700 cm^{-1}.
Melting point: 117°C.
Element analysis: as $C_{27}H_{34}N_3O_4Cl \bullet ½ H_2O$ (molecular weight of 525.05)
Theoretical values: C.61.77 : H.6,72; N.8.00; Cl.6.75
Observed values: C.61.46 : H.6.77; N.7.85; Cl. 6.64.
Mass: 515 (M) [superscript illegible]

(Practical Embodiment 2) (2S, 3S) –3- (3-methoxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)—chloro]-L-proline tert-butyl amide (Illustrative Compound Number 16) We stirred a tetrahydrofurane solution (2 ml) made up of 99.9 mg (0.262 mmol) of (2S, 3S)-3-amino-2-hydroxy-4- phenyl butanoyl-[4 (S) – chlor] – L proline tert-butyl amide; 97.0 mg (0.506 mmol) of EDC; 42.6 mg (0.256 mmol) of 3-methoxy-2-methyl benzoate; and 46.1 mg (0.341 mmol) of HOB at room temperature for 17 hours. We added an aqueous solution of saturated sodium hydrogencarbonate and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and then freeze-dried it. We obtained 101.3 mg (yield of 75 %) of the indicated compound as a colorless crystalline solid.

[0096] ^{1} H-NMR: δ ppm ($CDCL_3$, 270 MHz): 7.33-7.07 (m.6H), 6.86 (d,1H, J=8.1 Hz), 6.74 (d. 1H, J=8.1 Hz), 6.28 (s,1H), 6.05 (d.1H, J=8.31 Hz), 4.74-4.31 (m,4H), 4.09-3.92 (m, 1H), 3.88-3.67 (m, 1H), 2.88-2.40 (m, 4H), 1.98 (s.3H), 1.65 (s.1H), 1.30 (s.9H).
IR (KBr): 3327, 2965, 2923, 1649, 1583, 1455, 1383, 1366, 1313, 1262, 1226, 1101, 776, 752, 720 cm^{-1}.
Melting point 82-84°C
Element analysis: $C_{27}H_{34}N_3O_4Cl \bullet ½ H_2O$ (molecular weight of 525.05)
Theoretical values: C.61.77; H,6.72; N,8.00; Cl.6.75.

Observed values: C.61, 46; H, 6, 77; N,7, 85; Cl.6.64.
Mass: 529 $(M)^+$

(Practical Embodiment 3) (2S, 3S) –3 – (3-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S) – chlor]-L-proline tert-butyl amide (Illustrative Compound Number 8)
We stirred at room temperature a tetrahydrofurane solution (2 ml) made up of 94.1 mg (0.246 mmol) of (2S, 3S)-3 (S)-amino-2 (S)-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline-tert-butyl amide; 99.4 mg (0.519 mmol) of EDC; 43.5 mg (0.315 mmol) of 3-hydroxy benzoate; and 50.5 mg (0.374 mmol) of HOBt; for 21 hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. After washing the organic layers with saturated brine, we dried them with anhydrous sodium sulfate. Then we subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and then freeze-dried it. We obtained 85.5 mg (yield of 69 %) of the indicated compound as a colorless crystalline solid.

[0097] ^{1} H-NMR: δ ppm (CDCl[subscript illegible], 270 MHz): 8.25-6.46 (m.11H), 5.06-4.61 (m, 3H), 4.56-2.35 (m, 8H), 1.23 (s, 9H).
IR (KRr): 3406, 2968, 1648, 1585, 1530, 1454, 1367, 1272, 1226, 1116, 811, 751, 700, 751, 700 cm^{-1}.
Melting point: 112°C.
Element analysis: $C_{26}H_{32}K_3O_9Cl \bullet ½ H_2O$ (molecular weight of 511.02)
Theoretical values: C,61.11:H, 6.51; N,8.22; Cl,.6.94.
Observed values: C,61.25; H,6.55; N,7.95; Cl,.7.05.
Mass: 501 $(M)^+$

(Practical Embodiment 4) (2S, 3S)-3-(4-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 12)
We stirred at room temperature a tetrahydrofurane solution (2 ml) made up of 100.0 mg (0.262 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 113 mg (0.589 mmol) of EDC, 43.0 mg (0.311 mmol) of 4-hydroxy benzoate and 56. 1 mg (0.415 mmol) of HOBt for 20 hours. We added water and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers with saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it and obtained 78.0 mg (yield of 59 %) of the indicated compound as a colorless crystalline solid.

[0098] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 8.13-5.97 (m.12H), 4.69-4.20 (m.5H), 4.09-3.60 (m.3H), 2.95-2.43 (m.4H), 1.31 (s.9H).
IR (KBr): 3327, 2969, 2876, 1652, 1609, 1536, 1503, 1455, 1392, 1366, 1272, 1226, 1174, 1113, 851, 750 cm^{-1}.
Melting point: 106°C
Element analysis: $C_{26}H_{32}N_3O_5Cl \bullet ½ H_2O$ (molecular weight of 520.03)
Theoretical values: C,60.05; H,6.59; N,8.08; Cl,6.82
Observed values: C,60. 19; H,6.78; N,8.41; Cl,6.98.
Mass: 501$(M)^+$

(Practical Embodiment 5) (2S, 3S)-3-(2-methyl benzoyl) amino 2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 2)
We stirred at room temperature a tetrahydrofurane solution made up of 106. 2 mg (0.278 mmol) of (2S, 3S)-3-amino-2-hydroxy-1-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 112 mg (0.584 mmol) of EDC, 42.4 mg (0.311 mmol) of 2-methyl benzoate and 50 mg (0.37 mmol) of HOBt for four hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers with saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 54.0 mg (yield of 40 %) of the indicated compound as a colorless crystalline solid.

[0099] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.34-7.10 (m,9H), 6.27 (s,1H), 6.08 (d,1H, J=8, 4 Hz), 5.06-4.32 (m,4H), 4.14-3.61 (m, 3H), 2.93-2.41 (m,4H), 2.18 (s.,3H), 1.30 (s, 9H).
IR (KBr): 3322, 2968, 1649, 1530, 1455, 1392, 1366, 1270, 1207, 1112, 746, 700 cm^{-1}.
Melting point: 84°C.
Element analysis: $C_{27}H$[subscript illegible]N_3O_4Cl• ½ H_2O (molecular weight of 509.045)
Theoretical values: C,63.71; H,6.93; N,8.25; CL, 6.96
Observed values: C,63.39; H,6.52; N,7.90; Cl,7.08
Mass: 500 $(M+H)^+$

(Practical Embodiment 6) (2S, 3S)-3-(3-fluoro-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 18)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 110.4 mg (0.289 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide, 120 mg (0.626 mmol) of EDC, 1.2 mg (0.332 mmol) of 3-fluoro-2-methyl benzoate and 50 mg (0.37 mmol) of HOBt for ten hours. We added water and stopped the reaction. We diluted this reactive mixed solution using methylene chloride. We washed the organic layers with saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 70.6 mg (yield of 47 %) of the indicated compound as a colorless crystalline solid.
^{1} H-NMR: δ ppm (CHCl[subscript illegible], 270 MHz): 7.34-7.10 (m, 9H), 6.90 (d, 1H, J=7, 4Hz), 6.22 (s, 1H), 6.09 (d, 1H, J=8.4 Hz), 4.71-4.31 (m,4H), 4.16-3.68 (m, 3H), 2.89-2.42 (m, 3H), 2.05 (s, 3H), 1.30 (s, 9H).
IR (KBr): 3321, 2969, 2932, 1652, 1530, 1456, 1393, 1246, 1225, 1115, 830, 752, 700 cm^{-1}
Melting point: 86-88°C
Element analysis: $C_{27}H_{33}N_3O_4Cl$ • ½ H_2O (molecular weight of 527.036)
Theoretical values: C,61.53; H,6.51; N, 7.97; Cl,6.72; F,3.60
Observed values: C,61.18; H, 6.71; N,7.68; Cl, 6.62; F, 3.47
Mass: 517 $(M)^+$

(Practical Embodiment 7) (2S, 3S)-3-(3-hydroxy-4-methoxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 20)

We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 106.8 mg (0.280 mmol) of (2S, 3S)-3-amino-2-hydroxy-1-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 112 mg (0.584 mmol) of EDC, 52.4 mg (0.312 mmol) of 4-methoxy-3-hydroxy benzoate and 42.1 mg (0.312 mmol) of HOBt for 16 hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers with saturated brine. Then, we dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 70.6 mg (yield of 47 %) of the indicated compound as a colorless crystalline solid.
^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.35-7.01 (m,8 H), 6.88-6.10 (m, 4H), 4.74-4.31 (m, 3H), 4.18-3.60 (m, 4H), 2.96-2.40 (m, 3H), 1.29 (s, 9H).
Mass: 532 (M+H)[superscript illegible]
[Translator's note: "IR", "Melting Point", "Element analysis", "Theoretical Values" and "Observed Values" are not included in the original text for this Practical Embodiment]

(Practical Embodiment 8) (2S, 3S) –3-(3-formyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert butyl amide (Illustrative Compound Number 22)
We stirred at room temperature a tetrahydrofurane solution (5 ml) made up of 113.7 mg (0.298 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide, 121 mg (0.631 mmol) of EDC and 58 mg (0.43 mmol) of HOBt and 54.1 mg (0.360 mmol) of 3-formyl benzoate for five hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 83.9 mg (yield of 55 %) of the indicated compound as a colorless crystalline solid.
^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 10.02 (s, 1H), 8.80-6.24 (m, 11H), 5.06-4.30 (m, 4H), 4.10-3.64 (m, 3H), 2.90-2.34 (m, 4H), 1.32 (s, 9H).
IR (KBr): 3393, 2968, 2930, 2873, 1651, 1533, 1454, 1365, 1208, 1114, 936, 817, 748, 701 cm^{-1}
Melting point: 87°C
Element analysis: $C_{27}H_{32}N_3O_5Cl \bullet ½ H_2O$ (molecular weight of 523.029)
Theoretical values: C, 62.00; H,6,34; N,8.03; Cl, 6.78
Observed values: C,61.71; H,6.33; N, 8,66; Cl, 6.71
Mass: 514 $(M+H)^1$

(Practical Embodiment 9) (2S, 3S)-3-(3-fluorobenzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert butyl amide ((Illustrative Compound Number 10)
We stirred at room temperature a tetrahydrofurane solution (5 ml) made up of 124 mg (0.305 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert butyl amide, 163 mg (0.850 mmol) of EDC, 50.4 mg (0.365 mmol) of 3-fluoro benzoate and 63 mg (0.47 mmol) of HOBt for 18 hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride and washed the organic layers with saturated brine. Then, we dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 149.6 mg (yield of 91 %) of the indicated compound as a colorless crystalline solid.

^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.49-7.13 (m, 9H), 6.54 (d, 1H, J=8, 1Hz), 6.25 (s, 1H), 4.69-4.29 (m, 4H), 4.08-3.62 (m, 3H), 2.92-2.78 (m, 2H), 2.75-2.41 (m, 2H), 1.31 (s, 9H).
IR (KBr): 3337, 2969, 2932, 1649, 1455, 1366, 1271, 1224, 806, 751, 701 cm^{-1}
Melting point: 81-82°C
Element analysis: $C_{26}H_{31}N_3O_4ClF \bullet ¼ H_2O$ (molecular weight of 508.505)
Theoretical values: C, 61.41; H, 6.24; N,8.26; Cl, 6.97; F,3.4
Observed values: C, 61.40; H, 6.40; N,8.20; Cl, 6.74; F, 3.66.
Mass: 504 $(M+H)^+$

(Practical Embodiment 10) (2S, 3S)-3-(2-trifluoro methyl benzoyl) amino-2-hydroxy-4- phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 6)
We stirred at room temperature a tetrahydrofurane solution (5 ml) made up of 121.5 mg (0.318 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide, 126 mg (0.657 mmol) of EDC, 66.4 mg (0.347 mmol) of 2-trifluoro methyl benzoate and 54 mg (10.40 mmol) of HOBt for 23 hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and then dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 142.0 mg (yield of 81 %) of the indicated compound as a colorless crystalline solid.
^{1}H-NHR: δ ppm ($CDCl_3$, 270 MHz): 7.71-7.11 (m, 9H), 6.49-6.19 (m, 2H), 4.70-4.62 (m, 1H), 4.57-4.51 (m, 1H), 4.50-3.86 (m, 3H), 3.76-3.64 (m, 2H), 2.91-2.39 (m, 4H), 1.30 (s,9H).
IR (KBr): 3327, 2970, 2933, 1656, 1455, 1367, 1317, 1272, 1225, 1175, 1133, 1114, 1035, 771, 701 cm^{-1}.
Melting point: 88°C
Mass: 554 $(M+H)^+$

(Practical Embodiment 11) (2S, 3S)-3-(2-bromo-3-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 21)
We stirred at room temperature a tetrahydrofurane solution (5 ml) made up of 115.5 mg (0.302 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide, 121.4 mg (0.63 mmol) of EDC, 75.9 mg (0.350 mmol) of 2-bromo-3-hydroxy benzoate and 56.1 mg (0.415 mmol) of HOBt for 19 hours. We added a saturated sodium hydrogencarbonate aqueous solution and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. Then we washed the organic layers using saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 86.1 mg (yield of 49 %) of the indicated compound as a colorless crystalline solid.
^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.37-6.22 (m,10H), 5.06-4.60 (m, 3H), 4.53-4.31 (m, 2H), 4.24-3.43 (m, 3H), 2.99-2.39 (m, 3H), 1.30 (s, 9H).
IR (KBr): 3321, 2968, 2931, 1652, 1569, 1530, 1458, 1439, 1367, 1296, 1225, 1118, 1031, 873, 795, 750, 701 cm^{-1}.
Melting point: 117-118°C
Mass: 580 $(M+H)^1$

(Practical Embodiment 12) (2S, 3S)-3-(benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 1)
We stirred at room temperature a tetrahydrofurane solution (5 ml) made up of 116.0 mg (0.304 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 135 mg (0.704 mmol) of EDC, 47.4 mg (0.388 mmol) of benzoate [Translator's note: there appears to be a term missing before the word "benzoate"] and 46.2 mg (0.342 mmol) of HOBt for 22 hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 134.8 mg (yield of 91 %) of the indicated compound as a colorless crystalline solid.
^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.70-7.17 (m, 10H), 6.53 (d, 1H, J=8, OHz), 6.30 (s, 1H), 4.72-4.51 (m, 2H), 4.40-4.30 (m, 2H), 4.07-3.60 (m, 3H), 2.94-2.40 (m, 4H), 1.31 (s, 9H)
IR (KBr): 3413, 3340, 2968, 2931, 1648, 1531, 1488, 1454, 1391, 1366, 1272, 1226, 1113, 1074, 700 cm^{-1}.
Melting point: 85°C.
Element analysis: C[subscript illegible] $H_{32}N_3O_4Cl$• ½ H_2O (molecular weight of 495.018)
Theoretical values: C,63.09; H,6.72; N, 8.49; Cl,7.16
Observed values: C,63.32; H, 6.75; N, 8.49; Cl,6.89.
Mass: 486 $(M+H)^+$

(Practical Embodiment 13) (2S, 3S)-3-(2-naphthoyl)-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 51)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 111.2 mg (0.291 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide, 139 mg (0.725 mmol) of EDC, 58.4 mg (0.339 mmol) of 2-naphthalene carboxylate and 46.5 mg (0.344 mmol) of HOBt for six hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene l / methanol) and freeze-dried it. We obtained 134.8 mg (yield of 91 %) of the indicated compound as a colorless crystalline solid.

[0100] ^{1} H-NMR: δ ppm (CDCl[subscript illegible], 270 MHz):
8.19-6.29 (m, 14H), 5.06-2.42 (m, 11H), 1.32 (s, 9H).
IR (KBr): 3334, 2968, 1648, 1531, 1455, 1391, 1366, 1269, 1228, 1205, 1136, 1115, 778, 761, 701 cm^{-1}
Melting point: 95°C
Element analysis: C[subscript illegible] $H_{34}N_3O_4Cl$ • ¾ H_2O (molecular weight of 549.582)
Theoretical values: C,65.57; H, 6.51; N, 7.65; Cl, 6.45
Observed values: C, 65.69; H, 6.31; N, 7.52; C, 6.29.
Mass: 536 $(M+H)^+$

(Practical Embodiment 14) (2S, 3S)-3-(2-hydroxy-3-methoxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 17)

We stirred at room temperature a tetrahydrofurane solution (2 ml) made up of 86.1 mg (0.243 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 86.1 mg (0.449 mmol) of EDC, 41.5 mg (0.247 mmol) of 2-hydroxy-3-methoxy benzoate and 46.2 mg (0.342 mmol) of HOBt for four hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution with methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 98.0 mg (yield of 76 %) of the indicated compound as a colorless crystalline solid.

[0101] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 11.2 (s, 1H), 7.56-7.10 (m, 6H), 6.88-6.77 (m,1H), 6.27-6.14 (m, 1H), 4.67-4.27 (m, 4H), 4.09-3.82 (m, 4H), 3.74-3.65 (m, 3H), 2.94-2.41 (m, 3H), 1.32 (s, 9H)
IR (KBr): 3353, 2969, 2935, 1671, 1587, 1534, 1462, 1367, 1253, 1119, 936, 873, 779, 747, 702 cm^{-1}
Melting point: 120°C
Mass: 531 $(M)^+$

(Practical Embodiment 15) (2S, 3S)-3-(3-thenoyl) amino-2-hydroxy-4-phenyl butanoyl-14 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 27)
We stirred at room temperature a tetrahydrofurane solution (1.5 ml) made up of 90.8 mg (0.238 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-14 (S)-chlor]-L-proline tert-butyl amide, 102.4 mg (0.534 mmol) of EDC, 31.5 mg (0.246 mmol) of 3-thiophene carboxylate and 36.3 mg (0.269 mmol) of HOBt for two hours. We added a saturated sodium hydrogencarbonate aqueous solution and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 116.2 mg (yield of 99 %) of the indicated compound as a colorless crystalline solid.

[0102] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.82-7.24 (m, 1H), 7.37-7.16 (m, 7H), 6.63-6.27 (m, 2H), 4.70-4.28 (m, 4H), 4.06-3.89 (m, 2H), 3.81-3.59 (m, 2H), 2.91-2.41 (m, 3H), 1.31 (s, 9H).
IR (KBr): 3333, 2967, 2930, 1648, 1540, 1392, 1366, 1278, 1224, 1119, 873, 842, 747, 700 cm^{-1}
Melting point: 98°C
Element analysis: $C_{24}H$[subscript illegible] N_3O_4 ClS • ¼ H_2O (molecular weight of 496.543)
Theoretical values: C, 58.05; H, 6.19; N, 8.46; S, 6.46; Cl, 7.14.
Observed values: C, 58.19; H, 6.48; N, 7.94; S, 6.14; Cl, 6.77
Mass: 492 $(M)^+$

(Practical Embodiment 16) (2S, 3S)-3-(3-hydroxy-4-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 33)
We stirred at room temperature a tetrahydrofurane solution (1.5 ml) made up of 104.8 mg (0.274 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-14 (S)-chlor]-L-proline tert-butyl amide, 73.0 mg (0.381 mmol) of EDC, 40.6 mg (0.264 mmol) of 3-hydroxy-4-methyl benzoate

and 40.6 mg (0.300 mmol) of HOBt for one hour. We added a saturated sodium hydrogencarbonate aqueous solution and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 128.0 mg (yield of 93 %) of the indicated compound as a colorless crystalline solid.

[0103] IR (KBr): 3341, 2967, 2926, 1640, 1586, 1537, 1500, 1455, 1417, 1366, 1255, 1226, 1120, 873, 750, 701 cm^{-1}
Melting point: 122°C.
Mass: 516 $(M)^+$

(Practical Embodiment 17) (2S, 3S)-3-(3-furoyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 28)
We stirred at room temperature a tetrahydrofurane solution (8 ml) made up of 104.8 mg (0.274 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S) chlor]-L-proline tert-butyl amide, 75 mg (0.39 mmol) of 1-ethyl-3-(3-dimethyl aminopropyl) carboimide hydrochloride (aqueous carbodiimide), 35 mg (0.31 mmol) of 3-furane carboxylate and 42 mg (0.31 mmol) of HOBr for two hours. After we removed the solvent, we diluted it with ethyl acetate. We successively washed the organic layers using a 5 % sodium hydrogencarbonate aqueous solution and saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 100 mg (yield of 83 %) of the indicated compound as a colorless crystalline solid.

[0104] ^{1}H-MNR: δ ($CDCl_3$, 270 MHz): 7.88-7.13 (m,8H),. 6.80-6.30 (m, 3H), 4.66-4.24 (m, 4H), 4.10-3.61 (m, 2H), 2.92-1.86 (m, 4H), 1.30 (s, 9H).
IR (KBr): 3333, 3131, 2969, 2932, 1648, 1604, 1528, 1455, 1392, 1366, 1314, 1268, 1207, 1112, 1089, 1020, 876, 819, 753, 701, 602 cm^{-1}.
Melting point: 94-99°
Element analysis: $C_{27}H_{30}N_3O_5Cl \bullet 1/3\ H_2O$ (molecular weight of 481.959)
Theoretical values: C,59.81; H, 6.41; H, 8.72; Cl, 7.36.
Observed values: C, 60.09; H, 6.59; N, 8.71; Cl, 7.32
Mass: 476 $(M)^+$

(Practical Embodiment 18) (2S, 3S)-3-(2-ethyl-3-hydroxy-benzoyl)_amino-2-hydroxy-4-phenyl butanoyl-[4-(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 23)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 91.1 mg (0.239 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert butyl amide, 94.1 mg (0.491 mmol) of EDC, 35.1 mg (0.211 mmol) of 2-ethyl-3-hydroxy benzoate (see Reference 1) and 34.9 mg (0.258 mmol) of HOBt for 19 hours. We added saturated brine and stopped the reaction. Then, we diluted this reactive mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and

freeze-dried it. We obtained 97.4 mg (yield of 77 %) of the indicated compound as a colorless crystalline solid.

[0105] Melting point: 111-116°C

[0106] (Practical Embodiment 19) (2S, 3S)-3-(indole-2-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4-(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 70)
We dissolved 100 mg (0.26 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert butyl amide, 50 mg (0.31 mmol) of indole-2-carbonate and 42 mg (0.31 mmol) of HOBt in tetrahydrofurane (5 ml), added 75 mg (0.39 mmol) of EDC and stirred it at room temperature for six hours. We subjected the reactive mixture to reduced pressure, concentrated it and dissolved it using ethyl acetate. We successively washed it with a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine and then dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin-film chromatography (methylene chloride / methanol) and crystallized it using ether and hexane and obtained 104 mg (yield of 74 %) of the indicated compound as a colorless crystalline solid.

[0107] ^{1}H-NMR: δ ppm (CD_2OD, 270 MHz): 7.58 (m, 1H), 7.42-7.36 (m, 3H), 7.26-7.13 (m, 4H), 7.10-7.01 (m, 2H), 4.98-4.31 (m, 5H), 3.89-3.80 (m, 1H), 3.10-3.03 (m, 1H), 2.97-2.88 (m, 1H), 2.78-2.68 (m, 1H), 2.19-2.08 (m, 1H), 1.30 (s, 9H).
Melting point: 126-132°C
Element analysis: $C_{28}H_{33}N_4O_4Cl \bullet 1/3\ H_2O$ (molecular weight of 531.03)
Theoretical values: C, 63.33; H, 6.39; N, 10.55; Cl, 6.68
Observed values: C, 63.32; H, 6.14; N, 10.63; Cl, 6.79
Mass: 525 $(M+H)^+$

(Practical Embodiment 20) (2S, 3S)-3-(5-fluoro indole-2-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 75)
We dissolved 100 mg (0.26 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide, 42 mg (0.31 mmol) of 5-fluoro indole-2-carbonate and 42 mg (0.31 mmol) of HOBt, tetrahydrofurane (6 ml), added 75 mg (0.39 mmol) of EDC and stirred it for four hours at room temperature. We subjected the reactive mixture to reduced pressure, dissolved it using ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and crystallized it using ether and hexane. We obtained 101 mg (yield of 72 %) of the indicated compound as a colorless crystalline solid.

[0108] ^{1}H-NMR: δ ppm (CD_3OD, 270 MHz); 7.41-7.33 (m, 3H), 7.28-7.20 (m, 3H), 7.15-7.10 (m,1H), 7.04-6.93 (m,2H), 4.61-4.31 (m, 5H), 3.88-3.79 (m,1H), 3.09-3.01 (m, 1H), 2.97-2.87 (m, 1H), 2.78-2.71 (m, 1H), 2.18-2.08 (m, 1H), 1.30 (s, 9H).
Melting point: 169-171°C
Element analysis: C[subscript illegible]$H_{32}N_4O_4FCl \bullet 2/3\ H_2O$ (molecular weight of 555.03)
Theoretical values: C, 60.59; H, 6.05; N, 10.09; F, 3.42, Cl, 6.39

Observed values: C, 60.51; H, 5.55; N, 10.15; F, 3.30; Cl, 6.53
Mass: 543 $(M+H)^1$

(Practical Embodiment 21) (2S, 3S)-3-[(3-hydroxy-2-methyl) benzoyl] amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline benzyl amide (Illustrative Compound Number 93)
We dissolved 100 mg (0.22 mmol) of (2S, 3S) 3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline benzyl amide, 40 mg (0.26 mmol) of 3-hydroxy-2-methyl benzoate in tetrahydrofurane (6 ml), added 63 mg (0.33 mmol) of EDC and 34 m [one letter missing] (0.24 mmol) of triethyl amine and stirred it for four hours at room temperature. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol). We freeze-dried it and obtained 52 mg (yield of 43 %) of the indicated compound as a colorless crystalline solid.

[0109] ^{1}H-NMR: δ ppm (CD_3OD, 270 MHz): 7.40-7.17 (m, 10H), 6.94 (t, 1H, J=7.8Hz), 6.78-6.74 (m, 1H), 6.60 (d, 1H, J=7.6 Hz), 4.62-4.35 (m, 7H), 4.17-3.91 (m, 1H), 3.12 (dd,1H, J=3.3 Hz), 2.89-2.68 (m, 2H), 2.25-2.15 (m, 1H), 1.88, 1.84 (s,s,3H,2:7).
Melting point: 100-109°C
Element analysis: $C_{33}H_{22}N_3O_5Cl \bullet H_2O$ (molecular weight of 568.05)
Theoretical values: C, 63.43; H, 6.03; N, 7.40; Cl, 6.24
Observed values: C, 63,54; H, 5.91; N, 7.02; Cl, 5.98
Mass: 550 $(M+H)^+$

(Practical Embodiment 22) (2S, 3S)-3-[number illegible] (3-hydroxy-2-methyl) benzoyl] amino-2-hydroxy-4-phenyl butanoyl-14 (S)-chlor]-L-proline n-butyl amide (Illustrative Compound Number 94)
We dissolved 100 mg (0.26 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline n-butyl amide, 47 mg (0.31 mmol) of 3-hydroxy-2-methyl benzoate and 42 mg (0.31 mmol) of HOBt in tetrahydrofurane (6 ml) and stirred it for four hours at room temperature. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 85 mg (yield of 63 %) of a colorless crystalline solid.

[0110] ^{1}H-NMR: δ ppm (CD_3OD, 270 MHz): 7.35-7.17 (m, 5H), 6.97-6.91 (m, 1H), 6.78-6.73 (m, 1H), 6.60 (d, 1H, J=7, 7.3 Hz), 4.62-4.42 (m, 5H), 3.98-3.90 (m; 1H), 3.26-3.11 (m, 3H), 2.81-2.68 (m, 2H), 2.21-2.11 (m, 1H), 1.91, 1.84 (s,s, 3H, 1:11), 1.54-1.42 (m, 2H), 1.39-129 (m, 2H), 0.90 (t, 3H, J=7.25 Hz).
Melting point: 103-107°C

Element analysis: $C_{27}H$[subscript illegible]N[subscript illegible]$O_5Cl \bullet 2/3\ H_2O$ (molecular weight of 528.03)
Theoretical values: C,61.14; H, 6.75; K, 7.96; Cl, 6.71
Observed values: C, 61.29; H, 6.57; K, 7.71; Cl, 5.53
Mass: 516 $(M+H)^+$

(Practical Embodiment 23) (2S, 3S)-3-(4-ethyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 23)
We dissolved 107.4 mg (0.281 mmol) of (2S, 3S)-3-amino-hydroxy-4-phenyl butanoyl [4 (S)-chlor]-L-proline tert-butyl amide, 49.0 mg (0.326 mmol) of 4-ethyl benzoate and 55 mg (0.41 mmol) of HOBt in tetrahydrofurane (4 ml), added 113.1 mg (0.590 mmol) of EDC and stirred this for seven hours at room temperature. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chlorine. We washed the organic layers with saturated brine and then dried them using anyhydrous sodium. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 111.1 mg (yield of 77 %) of the indicated compound as a colorless crystalline solid.

[0111] ^{1} H-NMR: δ ppm (CDCl[subscript illegible], 270 MHz): 7.52-7.63 (m, 2H), 7.16-7.36 (m, 7H), 6.31-6.73 (m, 2H), 4.31-4.75 (m, 4H), 3.59-4.09 (m, 3H), 2.40-2.93 (m, 4H), 1.31 (s, 9H), 1.22 (t, 3H, J=8.0 Hz).
Melting point: 83-85°C
Element analysis: $C_{28}H_{36}N_3O_4Cl \bullet ¾\ H_2O_4$ (molecular weight of 523.072)
Theoretical values: C, 64.30; H, 6.94; N, 8.03; Cl, 6.78.
Observed values: C, 64.57; H, 7.09; N, 7.78; Cl, 6.61
Mass: 514 $(M+H)^+$

(Practical Embodiment 24) (2S, 3S)-3-(α-naphthoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S) chlor]-L-proline tert butyl amide (Illustrative Compound Number 50)
We dissolved 106.8 mg (0.280 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert butyl amide, 55.1 mg (0.320 mmol) of α-naphthylate and 60 mg (0.44 mmol) of HOBr in tetrahydrofurane (4 ml), added 104.1 mg (0.543 mmol) and stirred it for 17 hours at room temperature. We added saturated brine and stopped the reaction. We diluted this mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 133.4 mg (yield of 89 %) of the indicated compound as a colorless crystalline solid.

[0112] ^{1} H-NMR: δ ppm (CDCl[subscript illegible], 270 MHz); 7.77-7.99 (m, 3H), 7.21-7.51 (m, 9H), 6.28-6-65 (m, 2H), 4.33-4.82 (m, 4H), 3.60-4.19 (m, 4H), 2.42-2.94 (m, 3H), 1.31 (s, 9H).
Melting point: 89-91°
Element analysis: $C_{30}H_{34}N_3O_4\ Cl \bullet ¾\ H_2O$ (molecular weight of 549.582)
Theoretical values: C,65.56; H, 6;51; N, 7.65; Cl, 6.45
Observed values: C, 65.53; H, 6.23; N, 7.57; Cl, 6.57
Mass: 536 $(M+H)^+$

(Practical Embodiment 25) (2S, 3S)-3-(2-chlor-5 methyl thiobenzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert butyl amide (Illustrative Compound Number 95)
We dissolved 98.1 mg (0.267 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 62.0 mg (0.392 mmol) of 2-choro-5 methyl thiobenzoate and 53.0 (0.392 mmol) of HOBt in tetrahydrofurane (4 ml), added 96.4 mg (0.503 mmol) of EDC and stirred it for 17 hours at room temperature. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 135.4 mg (yield of 90 %) of the indicated compound as a colorless crystalline solid.

[0113] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.54-8.57 (m, 3H), 7.15-7.63 (m, 5H), 6.15-6.60 (m, 2H), 4.29-6.10 (m, 4H), 3.62-4.20 (m, 4H), 2.43-2.94 (m, 3H), 1.31 (s, 9H)
Melting point: 73-74°C
Mass: 602 $(M+H)^+$

(Practical Embodiment 26) (2S, 3S)-3-(3-(benzyl oxycarbonyl) amino-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S) chlor]-L-proline tert-butyl amide (Illustrative Compound Number 96)
We stirred at room temperature a tetrahydrofurane solution (12 ml) made up of 311 mg (0.814 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 314 mg (1.64 mmol) of EDC, 259 mg (1.15 mmol) of 3-(benzyl oxycarbonyl) amino-2-methyl benzoate and 55 mg (1.15 mmol) of HOBt for 14 hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 588.0 mg (yield of 100 %) of the indicated compound as a colorless crystalline solid.

[0114] ^{1}H-NMB: δ ppm ($CDCl_3$, 270 MHz): 7.12-7.85 (m, 12H), 6.85-6.94 (m, 1H), 6.13-6.48 (m, 2H), 5.19 (s, 2H), 4.29-4.69 (m, 5H), 3.70-4.13 (m, 3H), 2.39-2.87 (m, 4H), 1.95 (s, 3H), 1.30 (s, 9H).
Melting point: 100°C
Element analysis: C[subscript illegible]$H_{41}N_4O_6Cl$ • ½ H_2O (molecular weight of 658.194)
Theoretical values: C,63.87; H, 6.43; N, 8.51; Cl, 5.39
Observed values: C, 63.57; H, 6.01; N, 8.39; Cl, 5.19
Mass: 649 $(M+H)^+$

(Practical Embodiment 27) (2S, 3S)-3-(3-amino-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 97)
We stirred at room temperature in a hydrogen atmosphere 398.9 mg of (2S, 3S)-3-[3-(benzyl oxycarbonyl) amino-2-methyl benzoyl] amino-2-hydroxy-4-phenyl butanoyl [4 (S)-chlor]-L-proline tert-butyl amide and a methanol suspension (3.5 ml) of 56.4 mg of palladium black for 17 hours. We returned the reaction group to a nitrogen atmosphere and then diluted it using

methylene chloride. We filtered this diluted solution using cellite [phonetic] and removed the palladium black. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 238.60 mg (yield of 41 %) of the indicated compound as a colorless crystalline solid.

[0115] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 6.93-7.33 (m, 6H), 6.09-6.72 (m, 4H), 4.30-4.71 (m, 4H), 3.63-4.14 (m, 6H), 2.40-3.18 (m, 4H), 1.95 (t, 2H, J=22.5 Hz) 1.30 (s, 9H).
Melting point: 106-108°C
Mass: 515 $(M+H)^+$

(Practical Embodiment 28) (2S, 3S)-3-(2-iodobenzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 98)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 102.5 mg (0.268 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 102 mg (0.532 mmol) of EDC, 79.4 mg (0.320 mmol) of 2-iodobenzoate and 40.0 mg (0.296 mmol) of HOBt for one hour. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried it with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 123.2 mg (yield of 75 %) of the indicated compound as a colorless crystalline solid

[0116] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz):
7.78-7.85 (m, 1H), 7.19-7.38 (m, 6H), 7.03-7.13 (m, 2H), 6.22-6.53 (m, 2H), 4.31-4.75 (m, 4H), 3.64-4.10 (m, 4H), 2.40-2.93 (m, 3H), 1.30 (s, 9H)
Melting point: 94°C
Mass: 612 $(M+H)^+$

(Practical Embodiment 29) (2S, 3S)-3-(2-propyl-3-hydroxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl [4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 99)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 81.1 mg (0.212 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl [4 (S) chlor]-L-proline tert-butyl amide, 77.9 mg (0.406 mmol) of EDC, 41.6 mg (0.233 mmol) of 2-propyl-3-hydroxy benzoate (method is synthesis is indicated in Reference Example 1) and 34.5 mg (0.233 mmol) of HOBt. for six hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 77.8 mg (yield of 67 %) of the indicated compound as a colorless crystalline solid.

[0117] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 6.63-7.34 (m, 8H), 6.25 (s, 1H), 5.42 (s. 1H), 4.31-4.71 (m, 4H), 3.61-4.12 (m, 4H), 2.38-2.94 (m, 5H), 1.30 (s, 9H), 1.00 (1.3H, J=7.4 Hz).
Melting point: 108-112°C
Element analysis: $C_{29}H_{38}N_3O_5Cl \bullet H_2O$ (molecular weight of 562.106)

Theoretical values: C, 61.97; H, 7.17; N. 7.48; Cl, 6.31
Observed values: C, 62.14: H, 6.93; N,722: Cl, 6.60
Mass: 544 $(M+H)^+$

(Practical Embodiment 30) (2S, 3S)-3-((2-methyl)-α-naphthoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 100)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 100.3 mg (0.263 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4-(S)-chlor]-L-proline tert-butyl amide, 121.4 mg (0.633 mmol) of EDC, 53.3 mg (0.286 mmol) of (2-methyl)-α-naphthylate and 51.3 mg (0.380 mmol) of HOBt for 21 hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 76.4 mg (yield of 53 %) of the indicated compound as a colorless crystalline solid.

[0118] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.71-7.79 (m, 2H), 7.15-7.43 (m, 9H), 6.14-6.50 (m, 2H), 4.33-5.05 (m, 4H), 3.60-4.23 (m, 4H), 2.66-2.95 (m, 3H), 2.22-2.65 (m, 3H), 1.31 (s, 9H).
Melting point: 99°C
Element analysis: C[subscript illegible]H[subscript illegible]$N_3O_5CL\bullet H_2O$ (molecular weight of 562.106)
Theoretical values: C,61.97; H, 7.17; N, 7.48; Cl, 6.31
Observed values: C, 62.14; H, 6.93; N, 7.22; Cl, 6.60
Mass: 550 $(M+H)^+$

(Practical Embodiment 31) (2S, 3S)-3-(2-chlorobenzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 101)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 100 mg (0.262 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 100 mg (0.522 mmol) of EDC, 40.1 mg (0.256 mmol) of 2-chlorobenzoate and 39 mg (0.29 mmol) of HOBt for three hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 132.9 mg (yield of 97 %) of the indicated compound as a colorless crystalline solid.

[0119] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.17-7.48 (m, 8H), 6.69 (d, 1H), J=8.2 Hz), 6.28 (s,1H), 4.31-4.75 (m, 4H), 3.61-4.17 (m, 3H), 2.41-2.93 (m, 5H), 1.30 (s, 9H)
Melting point: 85°C
Element analysis: $C_{26}H_{31}N_3O_4Cl\bullet$ ½ H_2O (molecular weight of 529.463)
Theoretical values: C, 58.98; H, 6.09; N, 7.93; Cl,13.39.
Observed values: C, 58.62; H, 6.01; N, 7.64; Cl, 13.38
Mass: 520 $(M+H)^+$

(Practical Embodiment 32) (2S, 3S)-3-(9-acridine carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 102)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 104.3 mg (0.273 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S) chlor]-L-proline tert-butyl amide, 109.4 mg (0.571 mmol) of EDC, 66.1 mg (0.296 mmol) of 9-acridine carboxylate and 50 mg (0.37 mmol) of HOBt for three hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 69.1 mg (yield of 43 %) of the indicated compound as a colorless crystalline solid.

[0120] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 6.95-8.17 (m, 13H), 6.17-6.60 (m, 2H), 4.70-5.0 (m, 2H), 4.09-4.52 (m, 3H), 3.69-3.94 (m, 2H), 2.68-3.67 (m, 5H), 1.30 (s, 9H).
Melting point: 143°C
Element analysis: C[subscript illegible]H[subscript illegible]N_4O_4Cl• 3/2 H_2O (molecular weight of 614.141)
Theoretical values: C, 64.54; H, 6.24; N, 9.12; Cl, 5.77
Observed values: C, 64.35; H,5:91; N, 8.83; Cl,5.85
Mass: 587 $(M+H)^+$

(Practical Embodiment 33) (2S, 3S)-3-(2-propyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 103)
We stirred at room temperature a tetraohydrofurane solution (3 ml) made up of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 61.9 mg (0.323 mmol) of EDC, 27.1 mg (0.165 mmol) of 2-propyl benzoate (see Reference text J. A. Ch. cm. Soc, 113, 1991, 4931) and 25.7 mg (0.190 mmol) of HOBt. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 70.6 mg (yield of 81 %) of the indicated compound as a colorless crystalline solid.

[0121] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 6.99-7.36 (m, 9H), 6.04-6.46 (m, 2H), 4.32-4.73 (m, 4H), 3.65-4.14 (m, 3H), 2.41-2.91 (m, 6H), 1.42 (q, 2H, J=7.7 Hz), 1.30 (s, 9H), 0.80 (t,3H), J=7.7 Hz).
Melting point: 74°C
Element analysis: C[subscript illegible]$H_{38}N_3O_4Cl$• H_2O (molecular weight of 546.107)
Theoretical values: C, 63.78; H, 7.38; N, 7.69; Cl, 6.49
Observed values: C, 64.00; H, 7.20; N, 7.56; Cl, 6.83
Mass: 528 $(M+H)^+$

(Practical Embodiment 34) (2S,3S)-3-(2-bromobenzoyl) amino-2-hydroxy-4-phenyl butanoyl 4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 104)
We stirred at room temperature a tetrahydrofurane solution (3 ml) made up of 108.4 mg (0.284 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl

amide, 108 mg (0.563 mmol), 108 mg (0.563 mmol) of EDC, 61.4 mg (0.305 mmol) of 2-bromobenzoate and 43.9 mg (0.325 mmol) of HOBt for 18 hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 143.3 mg (yield of 89 %) of the indicated compound as a colorless crystalline solid.

[0122] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.51-7.59 (m, 1H), 7.18-7.35 (n, 8H), 6.26-6.61 (m, 2H), 4.31-4.74 (m, 4H), 3.64-4.10 (m, 4H), 2.40-2.92 (m, 3H), 1.30 (s, 9H).
Melting point: 91°C
Mass: 564 $(M+H)^+$

(Practical Embodiment 35) (2S, 3S)-3-(2,3-dimethyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl [4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 105)
We stirred at room temperature a tetrahydofurane solution (4 ml) made up of 111.3 mg (0.291 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 118 mg (0.616 mmol) of EDC, 51.4 mg (0.342 mmol) of 2,3-dimethyl benzoate for six hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 133.9 mg (yield of 90 %) of the indicated compound as a colorless crystalline solid.

[0123] ^{1} H-NMR: δ ppm (CDCl[subscript illegible], 270 HMz): 6.91-7.34 (m, 8H), 6.01-6.46 (m, 2H), 4.31-4.74 (m, 5H), 3.60-4.20 (m, 3H), 2.41-2.91 (m, 3H), 2.23 (s, 3H), 2.02 (s, 3H), 1.30 (s. 9H).
Melting point: 94°C
Element analysis: C[subscript illegible, possible "23"] $H_{36}N_3O_4Cl \bullet H_2O$ (molecular weight of 532.080)
Theoretical values: C, 63.21; H, 7.20; N, 7.90; Cl, 6.66.
Observed values: C, 63.44; H, 6.88; N, 7.71; C, 6.68.
Mass: 514 (M+H)[superscript illegible]

(Practical Embodiment 36) (2S, 3S)-3-(9-anthracene carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 106)
We stirred at room temperature a tetrahydrofurane solution (4 ml) made up of 110 mg (0.288 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 110 mg (0.574 mmol) of EDC, 72.4 mg (0.326 mmol) of anthracene carboxylate and 36.8 mg (0.272 mmol) of HOBt for seven hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 29.4 mg (yield of 17 %) of the indicated compound as a colorless crystalline solid.

[0124] Melting point: 112-116°C
Mass: 586 $(M+H)^+$

(Practical Embodiment 37) (2S, 3S)-3-(2-methyl-3-propionyl oxybenzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-propine tert butyl amide (Illustrative Compound Number 107)
We stirred at room temperature a tetraohydrofurane solution (4 mmol) made up of 122 mg (0.319 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4-(S)-chlor]-L-proline tert butyl amide, 129 mg (0.673 mmol) of EDC, 52.4 mg (0.252 mmol) of 2-methyl-3-propionyl oxybenzoate and 65 mg z(0.48 mmol) of HOBt for 246 [sic] hours. We added saturated brine and stopped the reaction. We diluted this reactive mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 129.6 mg (yield of 90 %) of the indicated compound as a colorless crystalline solid.
^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 6.98-8.78 (m, 8H), 6.15-6.41 (m, 2H), 4.30-4.70 (m, 4H), 3.60-4.19 (m, 4H), 2.41-2.90 (m, 5H), 1.94-2.03 (m, 3H), 1.30 (s, 9H) (s, 9H), 1.28 (t, 3H, J=3.8 Hz).
Melting point: 87°C
Element analysis: C[subscript illegible]H[subscript illegible, possibly "38"]$N_3O_6Cl \bullet H_2O$ (molecular weight of 590.117)
Theoretical values: C, 61.06; H, 6.83; K, 7.12; Cl, 6.01
Observed values: C, 61.19; H, 6.59; N, 7.05; Cl, 5.84
Mass: 572 (M+H)[superscript illegible]

(Practical Embodiment 38) (2S, 3S)-3-(3,5-dihydroxy benzoyl) amino-2-hydro-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 25)
We added regulation-three hydrochloric acid to a 1,4-dioxane solution of 161.4 mg (0.266 mmol) of the (2S, 3S)-3-(3,5-bismethoxy methoxy benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide which was obtained using the above-mentioned method and stirred it for 20 minutes at 50°C. After we added saturated brine, we diluted this reactive mixed solution using ethyl acetate. We successively cleansed the mixed solution using a saturated sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 91.4 mg (yield of 66 %) of the indicated compound as a colorless crystalline solid.

[0125] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 8.23-10.42 (m, 2H), 6.11-7.56 (m, 8H), 4.25-4.57 (m, 5H), 3.25-3.70 (m, 5H), 2.49-2.89 (m, 3H), 1.90-2.02 (m, 1H), 1.24 (s, 9H).
Melting point: 167-168°C
Mass: 518 $(M+H)^+$

(Practical Embodiment 39) (2S, 3S)-3-(2-hydroxy-3-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline amyl amide (Illustrative Compound Number 108)

We dissolved 196 mg (0.50 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline amyl amide, 91 mg (0.60 mmol) of 2-methyl-3-hydroxy benzoate and 68 mg (0.50 mmol) of HOBt in tetrahydrofurane (10 ml), added 114 mg (0.6 mmol) of EDC and stirred it at room temperature for 16 hours. We subjected the reactive mixture to reduced pressure and concentrated it, dissolved it using ethyl acetate, successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and crystallized it using ether and hexane. We obtained 138 mg (yield of 52 %) of the indicated compound as a colorless crystalline solid.

[0126] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 8.08 (s, 1H), 7.34-7.12 (m, 7H), 6.84-6.59 (m. 1H), 6.18-5.97 (m, 2H), 4.73-4.21 (m, 5H), 4.18-3.60 (m, 3H), 2.88-2.58 (m, 4H), 1.78-1.58 (m, 4H), 1.33-1.26 (m, 6H), 0.88-0.74 (m.3H).
Melting point: 69.7-76.1°C
Element analysis: C[subscript illegible]H33N_4O_4Cl • 3/2 H_2O (molecular weight of 557.09)
Theoretical values: C, 60.36; H, 6.51; N, 7.54; Cl, 6.36
Observed values: C, 59.72; H, 6.54; N, 7.81; Cl, 6.60.
Mass: 529 $(M+H)^+$

(Practical Embodiment 40) (2S, 3S)-3-(quinoline-3-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert butyl-amide (Illustrative Compound Number 60)
We dissolved 389 mg (1.02 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4-(S)-chlor]-L-proline tert-butyl amide, 181 mg (1.05 mmol) of 3-quinoline carbonate and 140 mg (1.04 mmol) of HOBt in tetrafurane (10 ml) and added 201 mg (1.05 mmol) of EDC and stirred it for five hours at room temperature. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and crystallized it using ether and hexane. We obtained 494 mg (yield of 92 %) of the indicated compound as a colorless crystalline solid.

[0127] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 9.11 (d, 1H, J=2.3 Hz), 8.35 (d, 1H, J=2.0 Hz), 8.11 (d, 1H, J=8.7 Hz), 7.88-7.76 (m, 2H), 7.65-7.55 (m, 1H), 7.34-7.18 (m, 5H), 6.97 (br.d, 1H, J=8.0 Hz), 6.39 (br.s. 1H), 4.78-4.32 (m, 5H), 4.17-3.96 (m, 2H), 3.01-2.84 (m, 2H), 2.73-2.61 (m, 2H), 1.39-1.23 (m, 9H).
Melting point: 103.4-116.6°C
Element analysis: C[subscript illegible]H[subscript illegible, possibly "38")N_4O_4Cl • ½ H_2O (molecular weight of 546.07)
Theoretical values: C, 63.80; H, 6.09; N, 10.28; Cl, 6.49
Observed values: C, 64.02; H, 6.37; N,10.08; Cl, 6.52
Mass: 537 $(M+H)^+$

(Practical Embodiment 41) (2S, 3S)-3-(quinoline-4-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 62)

We dissolved 386 mg (1.01 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4(S)-chlor]-L-proline tert-butyl amide, 177 mg (1.02 mmol) of 4-quinoline carboxylate and 141 mg (1.04 mmol) of HOBt in tetrahydrofurane (10 ml), added 198 mg (1.04 mmol) of EDC and stirred it at room temperature for five hours. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and crystallized it using ether and hexane. We obtained 428 mg (yield of 80 %) of the indicated compound as a colorless crystalline solid.

[0128] ^{1} H-NMR: δ ppm ($CDCl_3$, 270 MHz): 8.87 (d, 1H, J=4.1 Hz), 7.82-7.62 (m, 2H), 7.49-7.21 (m, 7H), 6.43 (br.d, 1H, J=8.4 Hz), 6.18 (br.s, 1H), 4.83-4.77 (m, 1H), 4.51 ((t., 1H, J=7.6 Hz), 4.37-4.33 (m, 2H), 4.20-3.88 (m, 2H), 3.78-3.70 (m, 1H), 2.94-2.58 (m, 4H), 1.37-1.22 (m, 9H)
Melting point: 93.6-105.1°C
Element analysis: C[subscript illegible]H[subscript illegible]$N_4O_4Cl \bullet H_2O$ (molecular weight of 555.08)
Theoretical values: C, 62.75; H, 5.99; N, 10.09; Cl, 6.39
Observed values: C,62.97; H, 6.45; N, 9.93; Cl, 6.55
Mass: 537 $(M+H)^+$

(Practical Embodiment 42) (2S, 3S)-3-(4-hydroxy-quinoline-2-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 64)
We dissolved 115 mg (0.3 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 62 mg (0.33 mmol) of 4-hydroxy quinoline-2-carboxylate and 40 mg (0.3 mmol) of HOBt in dimethyl formamide (5 ml), added 69 mg (0.36 mmol) of EDC and stirred it at room temperature for five hours. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and crystallized it using ether and hexane. We obtained 133 mg (yield of 79 %) of the indicated compound as a colorless crystalline solid.

[0129] ^{1} H-NMR: δ ppm (CD_3OD, 270 MHz) : 8.18 (d, J=8.2 Hz, 1H), 7.74-7-15 (m, 2H), 7.40-7.36 (m, 7H), 7.25 (dd, J=7.4, 7.7Hz, 1H), 7.17-7.13 (m, 1H), 6.72 (br.d, J=1 HZ, 1H), 4.59-4.54 (m, 2H), 4.50-4.40 (m, 3H), 3.85-3.81 (m, 1H), 3.10 (dd, J=2.1, 2.7 Hz, 1H), 2.99-2.86 (m, 4H), 2.80-2.73 (m, 1H), 2.16-2.09 (m, 1H), 1.33, 1.30 (s, 9H), 1:12).
Melting point: 156.5-158.5°C
Element analysis: C[subscript illegible]$H_{33}N_4O_5Cl \bullet ½ H_2O$ (molecular weight of 562.07)
Theoretical values: C, 61.97; H, 6.10; N, 9.97; Cl, 6.31
Analyzed values: C, 61.76; H, 5.89; N, 10.04; Cl, 6.29
Mass: 553 $(M+H)^+$

(Practical Embodiment 43) (2S, 3S)-3-(3-hydroxy pyridine-2-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 30)
We dissolved 115 mg (0.3 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 46 mg (0.33 mmol) of 3-hydroxy pyridine-2-carboxylate and 40 mg (0.3 mmol) of HOBt in dimethyl formamide (5 ml), added 69 mg (0.36 mmol) of EDC and stirred it for five hours at room temperature. We subjected the reactive mixture to reduced pressure and concentrated it. We added ethyl acetate and dissolved the residue. We successively washed it with a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate, subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and crystallized it with ether and hexane and obtained 84 mg (yield of 56 %) of the indicated compound as a colorless crystalline solid.

[0130] ^{1}H-NMR: δ ppm (CD_3, 270 MHz): 8.08 (d, J=1.1 Hz, 1H), 7.44-7.37 (m, 2H), 7.33 (d, J=7.1 Hz, 1H), 7.29-7.20 (m,3H), 7.17-7.12 (m, 1H), 4.59-4.55 (m, 1H), 4.51 (d, J=4.5 Hz, 1H), 4.45-4.38 (m, 3H), 3.81-3.77 (m, 1H), 3.08-3.03 (m, 1H), 2.99-2.86 (m, 1H), 2.77-2.64 (m, 2H), 2.19-2.12 (m, 1H), 1.32 (s, 9H), 0.91-0.88 (m, 1H).
Melting point: 88-94°C
Element analysis: $C_{25}H_{31}N_4O_5Cl$ (molecular weight of 503.00)
Theoretical values: C, 59.70; H, 6.21; N, 11.14; Cl, 7.25
Analyzed values: C, 60.01; H, 6.49; N, 10.58; Cl, 6.76
Mass: 504 $(M+H)^+$

(Practical Embodiment 44) (2S, 3S)-3-(6-hydroxy quinoline 2-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 109)
We dissolved 115 mg (0.3 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 48 mg (0.33 mmol) of 6-hydroxy quinoline-2-carboxylate and 40 mg (0.33 mmol) of HOBt in dimethyl formamide, added 69 mg (0.36 mmol) of EDC and stirred it at room temperature for five hours. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate. We successively washed it with a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol), crystallized it with ether and hexane and obtained 101 mg (yield of 67 %) of the indicated compound as a colorless crystalline solid.
^{1}H-NMR: δ ppm; (CD_3OD, 270 MHz): 7.64 (dd, J=7.5, 8.0 Hz, 1H), 7.34-7.32 (m, 2H), 7.26-7.22 (m, 3H), 7.19-7.13 (m, 1H), 6.72 (d, J=8, 6 Hz, 1H), 4.54-4.50 (m, 1H), 4.48-4.36 (m, 1H), 3.82-3.76 (m, 1H), 3.04 (dd, J=3.6, 3.7 Hz, 1H), 2.88 (dd, J=10.5 Hz, 1H), 2.78-2.71 (m, 1H), 1.31 (s, 9H).
Melting point: 137.5-139.4°C
Element analysis: $C_{25}H_{31}N_4O_5Cl \bullet H_2O$ (molecular weight of 521.02)
Theoretical values: C, 57.63; H, 6.38; N, 10.75; Cl, 6.80
Analyzed values: C, 58.05; H, 6.70; N, 10.53; Cl, 6.84
Mass: 503 $(M+H)^+$

(Practical Embodiment 45) (2S, 3S)-3-(7-methoxy benzofurane-2-carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide ((Illustrative Compound Number 82)
We dissolved 191 mg (0.5 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 96 mg (0.5 mmol) of 7-methoxy benzofurane-2-carboxylate and 54 mg (0.4 mmol) of HOBt in dimethyl formamide (5 ml), added 115 mg (0.6 mmol) of EDC and stirred it at room temperature for five hours. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate. We successively washed it with a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol), crystallized it with ether and hexane and obtained 227 mg (yield of 82 %) of the indicated compound as a colorless crystalline solid.

[0131] ^{1}H-NMR: δ ppm (CD_3OD, 270 MHz); 7.39-7.34 (m, 3H), 7.27-7.24 (m, 4H), 7.16-7.12 (m, 1H), 7.03-6.98 (m, 1H), 4.63-4.59 (m, 1H), 4.50 (d, J=5.2 Hz, 1H), 4.42-4.37 (m, 3H), 4.01 (s, 3H), 3.84-3.78 (m, 1H), 3.09-3.04 (m, 1H), 3.01-2.86 (m, 1H), 2.77-2.70 (m, 1H), 2.18-2.10 (m, 1H), 1.32, 1.30 (s, 9H, 1:5), 0.92-0.88 (m, 2H).
Melting point: 103-106°C
Element analysis: $C_{29}H_{34}N_3O_6Cl$ (molecular weight of 556.06)
Theoretical values: C, 62.64; H, 6.16; N, 7.56; CL, 6.38
Analyzed values: C, 63.03; H, 6.44; N, 7.17; Cl, 6.05
Mass: 556 $(M+H)^+$

(Practical Embodiment 46) (2S, 3S)-3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline 1.1-dimethyl-2-hydroxy ethyl amide (Illustrative Compound Number 110)
We dissolved 302 mg (0.44 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline 1.1-dimethyl-2-hydroxy ethyl amide, 115 mg (0.76 mmol) of 3-hydroxy-2-methyl benzoate and 82 mg (0.61 mmol) of HOBt in dimethyl formamide (10 ml), added 175 mg (0.91 mmol) of EDC and stirred it for six hours at room temperature. We subjected the reactive mixture to reduced pressure, concentrated it and dissolved it using ethyl acetate. We successively washed it with a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol), crystallized it with ether and hexane and obtained 189 mg (yield of 46.7 %) of the indicated compound as a colorless crystalline solid.

[0132] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.33-7.22 (m, 5H), 7.01-7.6.96 (m, 1H), 6.79-6.76 (m, 1H, 6.66 (d, J=7.6 Hz. 1H), 5.45 (br.s, 1H), 4.70-4.67 (m, 2H), 4.66-4.60 (m, 1H), 4.51-4.31 (m, 3H), 4.07-4.02 (m, 1H), 3.89 (d, J=6.4 Hz, 1H), 3.83-3.78 (m, 1H), 3.66-3.52 (m, 1H), 3.44-3.40 (m, 1H), 2.89-2.80 (m, 2H), 2.79-2.54 (m, 2H), 2.03-2.68 (s, 3H. 1:5), 1.27, 1.20 (s. 6H, 9:10), 0.91-0.80 (m. 1H).
Melting point: 117-119°C

Element analysis: C[subscript illegible]H[subscript illegible]$N_3O_6Cl \bullet 3/2\ H_2O$ (molecular weight of 559.06)
Theoretical values: C, 58.01; H, 6.67; N, 7.52; Cl, 6.34
Observed values: C, 58.54; H, 6.65; N, 7.09; Cl, 5.93
Mass: 532 $(M+H)^+$

(Practical Embodiment 47) (2S, 3S)-3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline-L-proline phenyl amide (Illustrative Compound Number 111)
1) We stirred at room temperature an ethylene chloride (5 ml) solution made up of 240 mg (0.961 mmol) of N-[one numeral illegible]-butoxy carbonyl-[4 (S)-chlor]-L-proline, 142 mg (1.52 mmol) of aniline, 222 mg (2.19 mmol) of triethyl amine and 178 mg (1.31 mmol) of isobutyl chloroformate for 19 hours. We added water and stopped the reaction. We diluted it with ethylene chloride and successively washed it with a 5 % citric acid aqueous solution, a saturated sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol) and obtained 351.9 mg (quantitative) of the indicated compound as a colorless crystalline solid.

[0133] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 6.93-7.62 (m, 6H), 4.48 (br, 2H), 4.07-4.18 (m, 1H), 3.74-3.96 (m, 2H), 2.68 (br, 1H), 1.49 (s, 9H).

2) (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline phenyl amide
We dissolved 351 mg of N-t-butoxy carbonyl-[4 (S)-chlor]-L-proline phenyl amide in a 1.4-dioxane solution ("regulation four", 3 ml) of hydrogen chloride and set it aside for 3 hours. After we stopped the reaction, we carried out azeotropy using benzene. We removed the hydrogen chloride and the 1,4-dioxane and obtained white crystals. We stirred at room temperature a tetrahydrofurane solution (6 ml) made up of these white crystals, 262 mg (0.887 mmol) of (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanate, 198 mg (1.96 mmol) of triethyl amine and 212 mg (1.57 mmol) of HOBt for 14 hours. We added saturated brine and stopped the reaction. Then, we diluted this mixed solution using methylene chloride and washed the organic layers with saturated brine and dried them with anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and obtained 358.4 mg (yield of 81 % of the indicated compound as a colorless crystalline solid.

[0134] ^{1}H-NMR: δ ppm (CDCl[subscript illegible], 270 MHz): 7.02-7.60 (m, 12H), 4.66-5.07 (m, 2H), 3.81-4.46 (m, 6H), 2.44-2.87 (m, 4H), 1.32 (s, 9H).

3) (2S, 3S)-3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline phenyl amide
We dissolved 137.9 mg of (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline phenyl amide in a solution of 1,4-dioxane ("regulation four", 1.5 ml) and set it aside for three hours. We stopped the reaction and then we carried out azeotropy using

benzene. We removed the hydrogen chloride and the 1,4-dioxane and obtained white crystals. We stirred at room temperature a tetrahydrofurane solution (2. ml) made up of these white crystals, 78 mg (0.51 mmol) of 3-hydroxy-2-methyl benzoate, 105 mg (0.548 mmol) of EDC, 65 mg (0.48 mmol) of triethyl amine and 65 mg (0.48 mmol) of HOBt for 24 hours. We added saturated brine and stopped the reaction. Then, we diluted this mixed solution using methylene chloride and washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and then freeze-dried it. We obtained 49.5 mg (yield of 20 %) of the indicated compound as a colorless crystalline solid.

[0135] ^{1}H-NMR: δ ppm (CD_3OD, 270 MHz): 6.60-7.58 (m, 15H), 4.48-4.99 (m, 5H), 3.94-4.03 (m, 1H), 2.19-3.71 (m, 9H).
Melting point: 120°C
Mass: 536 $(M+H)^+$

(Practical Embodiment 48) (2S, 3S)-3-[(3-hydroxy-2-methyl) benzoyl] amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline 4-fluoro benzyl amide (Illustrative Compound Number 112)
We dissolved 283 mg (0.6 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline 4-fluoro benzyl amide hydrochloride, 91 mg (0.6 mmol) of 3-hydroxy-2-methyl benzoate and 68 mg (0.5 mmol) of HOBt in dimethyl formamide (6 ml) and 126 mg (0.66 mmol) of EDC and 60 mg (0.6 mmol) of triethyl amine and stirred it at room temperature. We subjected the reactive mixture to reduced pressure and concentrated it. We dissolved it using ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride / methanol). We obtained 178 mg (yield of 52 %) of the indicated compound as a colorless crystalline solid.

[0136] ^{1}H-NMR: δ ppm (CD_3OD, 270 MHz): 7.34-7.19 (m, 7H), 7.00-6.91 (m, 3H), 6.75 (d, J=8.1 Hz, 1H), 6.60 (d, J=7.6 Hz, 1H), 4.59-4.32 (m, 6H), 4.12-4.07 (m, 1H), 3.99-3.93 (m, 1H), 3.11 (d, d, J=3.7, 3.7 Hz, 1H), 2.79-2.68 (m, 2H), 2.21-2.16 (m, 1H), 1.87, 1.83 (s.s., 3H). 1:12.
Melting point: 106-108°C
Element analysis: C[subscript illegible]$H_{31}N_3O_5ClF \bullet H_2O$ (molecular weight of 586.07)
Theoretical values: C, 61.48; H, 5.68; N, 7.17; Cl, 6.05; F, 3.24
Observed values: C, 61.73; H, 5.56; N, 7.15; Cl, 5.95; F, 3.17.
Mass: 568 $(M+H)^+$

(Practical Embodiment 49) (2S, 3)-3-(2,6-dimethyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide (Illustrative Compound Number 187)
We dissolved 111 mg (0.291 mmol) of (2S, 3S)-3-amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline tert-butyl amide, 73 mg (0.49 mmol) of 2,6-dimethyl benzoate and 70 mg (0.52 mmol) of HOBt in tetrahydrofurane (4 ml) and added 111 mg (0.579 mmol) of EDC and stirred it for three hours at room temperature. We added saturated brine and stopped the reaction. Then, we diluted this mixture with methylene chloride. We washed the organic layers with saturated

brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 101.5 mg (yield of 68 %) of the indicated compound as a colorless crystalline solid.

[0137] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 6.92-7.32 (m, 10H), 6.27 (s, 1H), 6.13 (d, 1H, J=8.1 Hz), 4.31-4.83 (m, 4H), 3.60-4.21 (m, 4H), 2.61-2.91 (m, 3H), 2.00 (s, 6H), 1.30 (s,9H).
Melting point: 95-96°C

[0138]
Element analysis: C[subscript illegible]$H_{36}N_3O_4Cl \bullet 2\ H_2O$ (molecular weight of 541.087)
Theoretical values: C, 62.15; H, 7.26; N, 7.77; Cl, 6.55
Observed values: C, 62.34; H, 6.98; N. 7.44; Cl, 6.72
Mass: 514 $(M+H)^+$

(Practical Embodiment 50) (2S, 3S)-3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S) chlor]-L-proline cyclopropyl amide (Illustrative Compound Number 153)
1) N-benzyl-oxycarbonyl [4 (S)-chlor]-L-proline cyclopropyl amide
We dissolved 1.36 g (4.78 mmol) of N-benzyl oxycarbonyl-[4 (S)-chlor]-L-proline, 0.40 ml (5.77 mmol) of cyclopropyl amine and 0.79 g (5.83 mmol) of HOBt in 50 ml of tetrahydrofurane and then added 1.07 g (5.58 mmol) of EDC and stirred it for 16 hours at room temperature. We subjected the reactive solution to reduced pressure and distilled it. We diluted the residue with ethylene chloride. We washed it successively using a 5 % citric acid aqueous solution, a saturated sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (n-hexane / ethyl acetate) and obtained 1.37 g of the indicated compound as a crystalline solid.

[0139] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.36(s, 5H), 6.44 (br, 1H), 5.30-5.08 (m, 2H), 4.44-4.36 (m, 2H), 3.97-3.64 (m, 2H), 2.67 (br, 2H), 1.59 (s,1H), 0.73 (d, J=6.1 Hz, 2H), 0.43 (br, 2H).
2) (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline cyclopropyl amide
We dissolved 500 mg (1.55 mmol) of N-benzyl oxycarbonyl-[4 (S)-chlor]-L-proline cyclopropyl amide in methanol (10 ml), added 153 mg of 10 % palladium carbon and stirred the reactive group for 20 hours while displacing the hydrogen gas. We filtered it, removed the catalyst, subjected the solvent to reduced pressure, removed it and obtained white crystals. We stirred at room temperature a dimethyl form [sic] solution (15 ml) made up of these white crystals, 534 mg (1.81 mmol) of (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanate, 0.30 ml (1.98 mmol) of DEPC and 0.30 ml (2.15 mmol) of triethyl amine at room temperature for six hours. We added saturated brine and stopped the reaction. We diluted this mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate and subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and obtained 616 mg of the indicated compound as a colorless crystalline solid.

[0140] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.35-7.13 (m, 5H), 6.65 (br.s, 1H), 4.85 (1H, d, J=8.7 Hz, 1H), 4.66-3.57 (m, 7H), 2.80-2.57 (m, 5H), 1.35 (s, 9H), 0.80-0.69 (m, 2H), 0.55-0.48 (m, 2H).

3) (2S, 3S)-3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline cyclopropyl amide

We dissolved 242 mg of (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline cyclopropyl amide in a 1,4 dioxane solution ("regulation four", 5 ml) of hydrogen chloride and stirred it for 30 minutes. We carried out azeotropy using benzene and removed the hydrogen chloride and the 1,4-dioxane and obtained white crystals. We stirred at room temperature a tetrahydrofurane solution (10 ml) made up of these white crystals, 115 mg (0.60 mmol) of 3-hydroxy-2-methyl benzoate, 105 mg (0.65 mmol) of EDC and 82 mg (0.61 mmol) of HOBt for 15 hours. We added saturated brine and stopped the reaction. We diluted this mixed solution using methylene chloride. We washed the organic layers using saturated brine and dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and freeze-dried it. We obtained 39 mg (yield of 15 %) of the indicated compound as a colorless crystalline solid.

[0141] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.37-7.19 (m, 6H), 7.06-6.81 (m, 2H), 4.80-4.69 (m. 2H), 4.58-4.13 (m, 4H), 3.97-3.92 (m, 1H), 3.52-3.31 (m, 4H), 3.04-2.96 (m, 1H), 2.76-2.07 (m, 4H), 1.44-1.31 (m, 2H), 0.74-0.51 (m, 2H), 0.48-0.32 (m, 2H).
Melting point: 129.1-140.3°C
Element analysis: $C_{26}H_{30}N_3O_5Cl \bullet H_2O$ (molecular weight of 535.93)
Theoretical values: C, 58.27; H, 5.64; N, 7.84; Cl, 6.62
Observed values: C, 58.34; H, 5.78; N, 7;64; Cl, 6.84
Mass: 500 $(M+H)^+$

(Practical Embodiment 51) (2S, 3S)-3-[(3-hydroxy-2-methyl) benzoyl] amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline cyclobutyl amide (Illustrative Compound Number 162)

1) N-4-butoxy carbonyl [4 (S)-chlor]-L-proline cyclobutyl amide

We dissolved 1 g (4.00 mmol) of N-t-butoxy carbonyl-[4 (S)-chlor]-L-proline in 50 ml of methylene chloride and then added 1.12 ml (8 mmol) of glacial trimethyl amine. Next, we added 0.62 ml (4.8 mmol) of isobutyl chloroformate while maintaining it at a temperature ranging from 0° to 5°C. We stirred this for one hour and then added 250m mg (3.51 mmol) of cyclobutyl amine and stirred it for one hour. We exposed the reactive solution to ice and diluted it using methylene chloride. We successively washed this using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We crystallized the resulting residue using hexane and obtained 0.45 mg of the indicated compound as a crystalline solid.

[0142] ^{1}H-NMR: δ ppm (CDCl[subscript illegible], 270 MHz): 6.66-6.40 (br, 1H), 4.56-4.40 (m, 2H), 4.37-4.28 (m, 1H), 3.89 (d, J=5.1 Hz 1H), 3.72-3.69 (br, 1H), 2.62 (br, 2H), 2,43-2.29 (m, 2H), 1.96-1.81 (m, 2H), 1.77-1.67 (m, 2H), 1.47 (s, 9H).
Melting point: 152-156°C

[0143]
Element analysis: $C_{14}H_{23}N_2O_3Cl$ (molecular weight of 302.791)
Theoretical values: C, 55.53; H, 7.66; N, 9.25; Cl, 11.71
Observed values: C, 55.40; H, 7.55; N, 9.22; 11.86
Mass: 303 $(M+H)^+$

2) (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline cyclobutyl amide
We dissolved 400 mg (1.32 mmol) of N-t-butoxy carbonyl-[4 (S)-chlor]-L-proline cyclobutyl amide in 5 ml of a "regulation four" hydrochloric acid / 1,4-dioxane solution and set it aside for one hour. We carried out azeotropy using benzene and removed the hydrogen chloride and the 1,4-dioxane and obtained white crystals. We stirred at room temperature a 10 ml tetrahydrofurane solution made up of these white crystals, 0.49 g (1.67 mmol) of (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanate, 0.19 ml (1.39 mmol) of triethyl amine, 0.27 mg (2 mmol) of HOBt and 0.48 g (2.50 mmol) of EDC for 20 minutes. We diluted this with ethyl acetate and successively washed it with a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (methylene chloride / methanol) and obtained 473 mg of the indicated compound as a colorless crystalline solid.

[0144] ^{1}H-NMR: δ ppm ($CDCl_3$, 270 MHz): 7.35-7.13 (m, 5H), 6.73-6.70 (br, 1H), 5.15-4.90 (d,d, 1:3, 1H), 4.60-4.54 (m, 1H), 4.49-4.03 (m, 5H), 3.85-3.77 (m, 1H), 3.71 (d, J=7.1 Hz, 1H), 2.82-2.73 (m, 2H), 2.67-2.62 (m, 2H), 2.33-2.18 (m, 2H), 1.87-1.78 (m, 2H), 1.66-1.59 (m, 2H), 1.42-1.35 (s.s, 1:2, 9H).
Melting point: 78-84°C

[0145] Element analysis: $C_{24}H_{34}N_3O_5Cl \bullet 1/3\ H_2O$ (molecular weight of 485.991)
Theoretical values: C, 59.31; H, 7.19; N, 8.65; Cl, 7.29
Observed values: C, 59.46; H, 6.95; N, 8.69; Cl, 7.26
Mass: 480 $(M+H)^+$

3) (2S, 3S)-3-(3-hydroxy-2-methyl benzoyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S)-chlor]-L-proline cyclobutyl amide
We dissolved 100 mg (0.21 mmol) of (2S, 3S)-3-(t-butoxy carbonyl) amino-2-hydroxy-4-phenyl butanoyl-[4 (S) chlor]-L-proline cyclobutyl amide in a 2 ml "regulation four" hydrochloric acid / 1,4-dioxane solution and set it aside for one hour. We carried out azeotropy using benzene, removed the hydrogen chloride and 1,4-dioxane and obtained white crystals. We stirred at room temperature a 4 ml tetrahydrofurane solution made up of these white crystals, 38 mg (0.25 mmol) of 3-hydroxy-2-methyl benzoate, 32 ml (0.23 mmol) of triethyl amine, 34 mg (0.25 mmol) of HOBt and 60 mg (0.32 mmol) of EDC for fifteen hours. We diluted this with ethyl acetate and successively washed it using a 5 % citric acid aqueous solution, a 5 % sodium hydrogencarbonate aqueous solution and saturated brine. Then, we dried the organic layers using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using thin film chromatography (methylene chloride /

methanol), [Translator's note: a word has been omitted here; however, based on the preceding text, the word is most likely "crystallized"] it using hexane and obtained 47 mg (yield of 45.5 %) of a colorless crystalline solid.

[0146] ^{1}H-NMR: δ ppm (CD_3OD, 270 MHz): 7.36-7.18 (m, 5H), 6.98-6.92 (m, 1H), 6.78-6.73 (m, 1H), 6.61-6.56 (m, 1H), 4.61-4.41 (m, 5H), 4.35-4.23 (m, 1H), 3.96-3.88 (m, 1H), 3.31 (d, d,.J=1.9 Hz), 2.87-2.72 (m, 2H), 2.32-2.21 (m, 2H), 2.18-2.01 (m, 1H), 1.99-1.88 (m, 1H), 1.84 (s, 3H) 1.76-1.66 (m, 2H), 0.92-0.87 (br, 1H).
Melting point: 129-134°C

[0147]
Element analysis: $C_{27}H_{32}H$[subscript illegible"3"]O_5 Cl [term is missing here] (molecular weight of 514.0)
Theoretical values: C, 63.09; H, 6.28; N, 8.18; Cl, 6.90
Observed values: C, 63.04; H, 6.65; N, 7.97; Cl, 6.72
Mass: 514 $(M+H)^+$

(Reference Embodiment 1) 2-ethyl-3-hydroxy benzoate-2-ethyl-3-benzyl oxybenzaldehyde
We reacted 3-hydroxy benzaldehyde and benzyl bromide in the presence of potassium carbonate at room temperature in dimethyl formamide (reference text: **Journal of the American Chemical Society**, 116, 8402 (1994) and made benzyl ether. We added 4.53 ml (11.3 mmol) of butyl lithium to a toluene solution (12 ml) made up of 1.216 g (11.9 mmol) of N, N, N[superscript illegible] trimethyl ethylene diamine at 0°C. We immediately brought this to room temperature and stirred it as is for 40 minutes. We again cooled it to 0°C and slowly dropped a toluene solution (14 ml) of 2.290 g (10.79 mmol) of 3-benzyl oxybenzaldehyde. We immediately brought it to room temperature and stirred it for one hour as is. Next, we added 18.0 ml (32.4 mmol) of phenyl lithium (1.8.M cyclohexane-ether solution) at 0°C. We immediately brought it to room temperature and stirred it for three hours. Then, we added tetrahydrofurane (8 ml), cooled this reactive solution to -78°C and slowly dropped 5.2 ml (65 mmol) of ethyl iodide. We brought it to room temperature and then stirred it as is for seven days. We added saturated brine and stopped the reaction. Then we extracted the product using ethyl acetate. We washed the organic layers with saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (hexane / methylene chloride / ether-8 : 1 : 1) and obtained 1.371 g (yield of 53 %) of the indicated compound as a colorless crystalline solid.

[0148] ^{1}H-NMR ppm [Translator's note: the term "δ", which has always appeared thus far in this section, is missing from the text here] (CDCl[subscript illegible], 270 MHz): 10.33 (s, 1H), 7.80-7.23 (m, 7H), 7.15-7.09 (m, 1), 3 (m, 7H), 5.13 (s, 2H), 3.17 (q, 2H, J [sign here is illegible] 7.5 Hz), 1.23 (t, 3H, J [sign here is illegible] 7.3 Hz).

2-ethyl-3-benzyl oxy methyl benzoate
We added an acetone solution (4 ml) of 1.529 g (21.7 mmol) of 2-methyl-2-butene to an acetone solution (14 ml) of 1.370 g (3.70 mmol) of 2-ethyl-3-benzyl oxybenzaldehyde. We cooled the reactive solution to 0°C and then added an aqueous solution (15 ml) of 1.540 g (17.0 mmol) of sodium dihydrogen phosphate and 2.052 g (17.1 mmol) of sodium chlorite aqueous solution. We

immediately brought this to room temperature and stirred it as is for 20 hours. We brought the pH of the reactive liquor to approximately 1 and then extracted it with ethyl acetate. We successively washed the organic layers with a sodium thiosulfate aqueous solution and saturated brine. Then, we dried them using anhydrous sulfate. We subjected the solvent to reduced pressure and removed it. We applied the residue obtained as is to the next reaction.

2-ethyl-3-benzyl oxy methyl benzoate
We dissolved 1.73 g of 2-ethyl-3-benzyl oxymethyl benzoate in a mixture of benzene (12 ml) and methanol (3 ml) and slowly dropped a 10 % trimethyl silyl [phonetic] diazomethane / hexane solution (14 ml) at room temperature. We stirred it for one hour and then subjected it to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (hexane / ethyl acetate-9 : 1) and obtained 435 g (yield of 79 %) of the indicated compound as a colorless crystalline solid.

[0149] ^{1} H-NMR ppm ($CDCl_3$ 270 MHz): 7.50 (d, 1H, J=8 Hz), 7.37-7.19 (m, 5H), 7.04-6.97 (m, 2H), 5.09 (d, 1H, J=10.1 Hz), 5.06 (d, 1H, J=10.1 Hz), 3.86 (s. 3H), 2.11-1.81 (m, 2H), 1.00 (t, 3H, J=3 Hz)

2-ethyl-3-hydroxy methyl benzoate
We added a methanol solution (10 ml) of 1.430 g (5.29 mmol) of 2-ethyl-3-benzyl oxy methyl benzoate to a methanol suspension (12 ml) of 217 mg of 5 % palladium carbon powder. We stirred it in a hydrogen atmosphere for five days. We replaced the inside of the reactor with nitrogen and diluted it with methylene chloride. Then, we removed the palladium catalyst, subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (hexane / methylene chloride / ether = 7 : 2 :1) and obtained 540.9 mg (yield of 57 %) of the indicated compound as a colorless crystalline solid. We recovered 202.2 mg (14 %) of the unreacted raw material.

[0150] 2-ethyl-3-hydroxy benzoate
We dissolved 159.7 mg (0.886 mmol) of 2-ethyl-3-hydroxy methyl benzoate in a mixture of tetrahydrofurane (1 ml), methanol (1 ml) and water (1 ml). We added 72.4 mg (4.11 mmol) of lithium hydroxide-hydrate and stirred it at room temperature for four days. We oxidized the reactive solution and then extracted it using ethyl acetate. Then, we successively washed the organic layers using saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (hexane / ethyl acetate = 7 : 3) and obtained 35.1 mg (yield of 24 %) of the indicated compound as a colorless crystalline solid. We recovered 95.1 mg (60 %) of the unreacted raw material.

[0151] ^{1} H-NMR ppm ($CDCl_3$, 270 MHz): 8.61 (br, 1H), 7.35 (dd,1H, J1=8.1, J2=1.3 Hz), 7.09 (dd, 1H, J1=J2=8.1 Hz), 7.04 (dd, 1H, J1=8.1, J2=1.3 Hz), 3.00 (q, 2H, J=7.5 Hz), 1.17 (t, 3H, J=7.5 Hz).
1R (KBr): 3333, 3131, 2969, 2932, 1648, 1604, 1528, 1455, 1392, 1366, 1314, 1268, 1207, 1112, 1089, 1020, 876, 819, 753, 701, 602 cm^{-1}
Melting point: 158-162°C

(Reference Embodiment 2) 3-hydroxy-2-propyl benzoate

3-benzyl oxy-2-propyl aldehyde

We reacted 3-hydroxy benzaldehyde and benzyl bromide in the presence of potassium carbonate at room temperature in a DMF (Reference text: **Journal of the American Chemical Society,** 116, 8402, 1994) and produced benzyl ether. We added 5.46 ml of toluene [solution] made up of N, N, N[superscript illegible] trimethyl ethylene amine at 0°C. We immediately brought it to room temperature and stirred it as is for 40 minutes. We cooled it again to 0°C. Then, we slowly dropped a toluene solution (25 ml) of 2.761 g (13.01 mmol) of 3-benzyl oxy benzaldehyde. We immediately brought it to room temperature and stirred it as is for 40 minutes. Next, we added 40 ml of phenyl lithium (1.0 M cyclohexane-ether solution) at 0°C and immediately brought it to room temperature. We stirred it for three hours as is and then added tetrahydrofurane (10 ml). We cooled this reactive liquor to -78°C, added 8.9 ml (91.3 mmol) of propyl iodite, immediately brought it to room temperature and stirred it for 21 hours. We added saturated brine and stopped the reaction. Then, we extracted the product using ethyl acetate. We washed the organic layers with saturated brine and dried them using sodium sulfate [Translator's note: the word "anhydrous", which has been consistently used thus far, is missing here]. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (hexane / methylene chloride / ethyl ether = 8 /1 / 1) and obtained 2.239 g (yield of 68 %) of the indicated compound as a colorless crystalline solid.

[0152] Mass: 254 (M^+)

3-benzyl oxy-2-propyl benzoate

We added 2.6 g (29.1 mmol) of 2-methyl-2-butene to 2.237 g (8.80 mmol) of 3-benzyl oxy-2-propyl aldehyde at room temperature. We cooled the reactive liquor to 0°C and then added 3.490 (29.1 mmol) of sodium dihydrogenphosphate and 2.450 g (27.1 mmol) of sodium chlorite. We immediately brought it to room temperature and stirred it for 16 hours. We brought the pH of the reactive solution to approximately 1 and then extracted it using ethyl acetate. We successively washed the organic layers using a saturated sodium thiosulfate aqueous solution and saturated brine. Then, we dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it and used the residue obtained as is for the next reaction.

[0153] 3-benzyl oxy-2-propyl methyl benzoate

We added a 10 % trimethyl silyl [phonetic] diazomethane methanol solution (25 ml) to a benzene--methanol solution (25 ml) of 2.78 g (1.03 mmol) of 3-benzyl oxy-2-propyl benzoate at room temperature. We stirred it for 15 minutes and then subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (hexane / ethyl acetate- 9 /1) and obtained 2.438 g (yield of 83 %) of the indicated compound as a colorless crystalline solid.

[0154] Mass: 284 (M^+)

3-hydroxy-2-propyl methyl benzoate

We added a methanol solution (5 ml) of 577.8 mg (2.03 mmol) of 3-benzyl oxy-2-propyl methyl benzoate to a methanol suspension (2 ml) of 217 mg of 5 % palladium-carbon powder and stirred it in a hydrogen atmosphere for 17 hours. We replaced the inside of the reactor with nitrogen. Then, we diluted it using methylene chloride. We subjected the solvent to reduced

pressure and removed it. We refined the resulting residue using silica gel column chromatography (hexane / ethyl acetate = 8 : 2) and obtained 195.5 g (yield of 50 %) of the indicated compound as a colorless crystalline solid.

[0155] ^{1}H-NMR: δ ppm (CDCl[subscript illegible], 270 MHz): 7.39 (d, 1H, J=7.9 Hz), 7.11 (dd, 1H, J=7.9 Hz), 6.93 (d.1H, J=7.9 Hz), 3.89 (2, 3H), 2.92-2.86 (m, 2H), 1.69-1.54 (m, 2H), 1.28 (t, 3H, J=7.4 Hz)
IR (KBr): 3413, 1698 cm^{-1}
Element analysis: $C_{11}H_{14}O_3$ (molecular weight of 194.23)
Theoretical values: C, 68.02; H, 7.27
Observed values: C, 67.85; H, 7.53

3-hydroxy-2-propyl benzoate
We dissolved 115.8 mg (0.596 mmol) of 3-hydroxy-2-propyl methyl benzoate in a mixture of methanol (1 ml) and water (1 ml). We added 125.3 mg (2.99 mmol) of lithium hydroxide-hydrate and stirred at 100°C for four hours. We brought the pH of the reactive solution to approximately 1 and extracted it using ethyl acetate. We successively washed the organic layers using saturated brine and then dried them using anhydrous sodium sulfate. We subjected the solvent to reduced pressure and removed it. We refined the resulting residue using silica gel column chromatography (ethyl acetate) and obtained 91.4 mg (yield of 85 %) of the indicated compound as a colorless crystalline solid.

[0156] ^{1}H-NMR: δ ppm (CDCl[subscript illegible, possibly "3"], 270 MHz): 7.40 (d, 1H, J=7.9 Hz), 7.12 (dd, 1H, J=7.9 Hz), 6.99 3(d, 1H, J=7.9 Hz), 3.77 (s, 3H), 2.92-2.86 (m, 2H), 1.69-1.54 (m, 2H), 1.30 (t, 3H, J=7.4 Hz).
IR (KBr) 3386, 1699 cm^{-1}
Element analysis: C[subscript illegible]$H_{12}O_3$ (molecular weight of 180.20)
Theoretical values: C, 66.65; H, 6.71
Observed values: C, 66.41; H,6.81
Melting point: 144-145°C

(Formulation Embodiment 1) (Hard capsule formulation)
We packed 100 mg of the compound in Practical Embodiment 1 in powdered form, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate into each of the preparatory two-part hard gelatin capsules to manufacture unit capsules, washed and dried them.

[0157] (Formulation Embodiment 2) (Soft capsule formulation)
We manufactured a mixture of the compound indicated in Practical Embodiment 1 which was placed in a digestive oily matter such as soybean oil, cottonseed oil or olive oil, injected it into the gelatin using a positive displacement pump, obtained a soft capsule containing 100 mg of the active ingredients, washed and dried it.

[0158] (Formulation Embodiment 3) (Tablets)
We manufactured [the tablets] using the usual method using 100 mg of the compound indicated in Practical Embodiment 1, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of crystallite cellulose, 11mg of starch and 98.8 mg of lactose.

[0159] The surface of the tablets may be coated as needed.

[0160] (Formulation Embodiment 4) (Injection)
We manufactured this by stirring 1.5 weight % of the compound indicated in Practical Embodiment 1, stirred it in 10 capacity % propylene glycol. Then we brought it to a constant capacity by injecting water and sterilized it.

[0161] (Formulation Embodiment 5) (Suspension)
We manufactured this by placing 100 mg of the compound indicated in Practical Embodiment 1 in pulverized form, 100 mg of sodium carboxy methyl cellulose, 5 mg of sodium benzoate, 1.0 g of a sorbitol solution (Japanese Pharmacopoeia) and 0.025 ml of vanillin in 54 ml [Translator's note: 54 ml of what is not indicated here].

[0162] (Test Embodiment 1)
Measuring HIV Protease Inhibition Activity
We found the HIV protease inhibition activity of the peptide derivative in the present invention using the HIV protease manifested in the E. coli [colibacillus] and the synthesized matrix using the IC_{50} value as an index as follows.

[0163] a) Creating A Manifestation Vector
From the BH10 clone (mentioned in Flossie Wong-Staal, et al., **Nature**, vol. 313, pages 227-284, 1985) which comprised the main portions of the HTLV IIIB provirus, we cut out a field in the ClaI site in the gag field of the same virus and a field in the E coli site in the pol field. We inserted the fragment obtained in the same pBR 322 site and cloned it.

[0164] Next, we inserted a fragment made up of the base sequence:

GATCCTACCAAGTGATGGGTGCGAGAGCGTCAGTATTAAGCGGGGGAGAATTAGAT
GATGGTTCACTACCCACGCTCTCGCAGTCATAATTCGCCCCCTCTAATCTAGC

of the fragment which comprises the genetic translation initiation codon (ATC) between the BamHI and the ClaI sites which exist 5' upstream of the insertion site for this and we inserted the T7 promoter field [mentioned in (**Bgl 11 ~ BamHI Fragments**), Barbara A. Moffatt et al., **Journal of Molecular Biology**, vol 189, pages 113-130, 1986] in the same BamHI site.

[0165] We cut away the Bg1[part of term is missing from Japanese text] 1I site in the resulting plasmid (field on most upstream part of pol field) and carried out repair synthesis using a "klenow" fragment. Next, we recombined this using a T4 DNA ligase and constructed a manifestation vector pT7 HIV.GP (-) comprising the HIV gag field and the pol field.

[0166] b) Manifestation in E. coli
We introduced the pT7 HIV.GP (-) to the E. coli BL-21 [mentioned in (**DE-3**), Barbara A. Moffatt et al., **Journal of Molecular Biology**, vol. 189, pages 113-130, 1986] which comprised the T7 polymerase genes and cultivated the resulting transformant in an M9CA-10 % LB culture medium containing 200 μ g / ml ampicillin at 37°C until the absorbance at 600 nm reached 2

[0167] We added 0.4 mM of an isopropyl thio-β-D-galactoside and continued to cultivate it for three hours.

[0168] We gathered the resulting mycobionts, used them as a pallet and preserved them at 80°C.

[0169] The polyprotein synthesized from this manifestation vector is decomposed in the mycobionts through autodigestion and produces the HIV protease.

[0170] c) Refining
We suspended the mycobionts obtained from 2 liters of the culture solution in 60 ml of buffer A [50 mM of tris hydrochloric acid (pH of 7.5), 1mM of "dithioslatol" [phonetic], 0.7 % lysozyme, 10 μ g / ml of aprotinin, 5 mM of ethylene diamine tetraacetate, 10 μ g / ml of benzamide, 1 mM of phenyl fluoride methyl sulfonate and 10 % glycerol] and set it aside for ten minutes at 0°C. Then, we added Triton X-100 (0.1 %) and again set it aside for ten minutes at 0°C.

[0171] We carried out freeze-thawing four times, added DNase I (0.1 mg), 10 mM of magnesium chloride and decomposed the DNA in the suspension.

[0172] We took the supernatant obtained by centrifuging this suspension, attached it to a DEAE Sephadex A25 column (5 cm inside diameter x 20 cm) and carried out fractionation. This column was used for equalization using buffer B [50 mM-HEPES (pH of 7.8), 1 mM of "dithioslatol" [phonetic], 10 μ g / ml of aprotinin, 5 mM of ethylene diamine tetraacetate, 10 μ g / ml of benzamide, 1 mM of phenyl fluoride methyl sulfonate and 10 % glycerol].

[0173] We immediately gathered the fractions whose activity had been confirmed, carried out ammonium sulfate precipitation (60 %), dissolved the resulting precipitate in 2 ml of buffer C [50 mM of tris hydrochloric acid (pH of 7.5), 1 mM of "dithioslatol" [phonetic], 1 mM of ethylene diamine tetraacetate and 200 mM of sodium chloride], attached it to a TSK. S 2000 SW gel filter column (7.5 mm inside diameter x 60cm; manufactured by Tosoh Ltd.) and carried out fractionation using buffer C at a flow velocity of 0.5 ml / minute.

[0174] We concentrated to 200 % the resulting activated fractions using an ultrafiltration membrane with a fractionation molecular weight of 10,000, made an enzyme solution and preserved it at 80°C.

[0175] d) Measuring Activity
HIV protease inhibition activity was measured based on the method used by E.D. Matayoshi et al. (**Science**, 247, 954 (1990).

[0176] Specifically, we prepared a reactive solution of 50 mM of sodium acetate (pH of 5.5)- 1M brine containing the compound being studied--at a variety of concentrations--which had been dissolved in 20 μ M of synthetic matrix 4 (4 dimethyl aminoophenyl azo) benzoate (DABCYL)-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-5-[(2-aminoethyl) amino] naphthalene-1-sulfonate (EDANS) (manufactured by BACHEM Ltd.) and dimethyl sulfoxide. To this we added a reactive solution of partially refined recombinant HIV protease. We initiated the reaction at room temperature

and measured the reaction product using a fluorospectrophotometer. We calculated the amount of reaction product per unit hour in the presence of the compound being studied--at a variety of concentrations—and determined a 50 % inhibition concentration (1 [rest of item in parentheses is illegible].

[0177] The compound in the present invention exhibited outstanding HIV protease inhibition activity.

[0178] (Test Embodiment 2)
Inhibition of virus emission from HIV infected CEM cells
(Methodology) We washed the persistent HIV (HTLVIIIB) infected cells Mol t 4 cells (Mol t 4 / HTLVIIIB) twice using an RPMI 1640 culture medium (containing 10 % inactivated fetal calf serum). Then, we planted them in the same culture medium so that it reached a concentration of 1×10^5 cells / ml and cultivated them under 5 % carbonic acid [carbon dioxide] gas. 72 hours later, we obtained a supernatant of the culture through centrifugation and made a virus stock. We adjusted the CEM cells so that they reached 2×10^5 cells / ml using an RPMI 1640 culture medium (containing 10 % inactivated fetal calf serum) and added a virus stock which had been diluted to an appropriate concentration. We again added the compound at a variety of concentrations and cultivated this at 37°C in 5 % carbonic acid [carbon dioxide] gas. Seven days later, we collected the supernatant of this culture, measured the amount of HIV antigens contained therein using the EIA method (HIV antigens, EIA II, Abbot). The concentration at which 90 % of the emission was inhibited by adding the compound was IC_{90}.

[0179] The compound in the present invention markedly inhibited virus emission from the HIV infected CEM cells.

[0180] (Test Embodiment 3) The compound in the present invention exhibits pharmacodynamic characteristics which can be expected to bring out to the fullest extent the aforementioned inhibition action *in vivo*. For example, when 10 mg / kg of the compound in the present invention was administered intravenously to rats, the level of the drug in the blood one hour after administration was either nearly the same as the ED_{90} value in the cell test or higher. The concentration of the drug detected in the blood of the rats 30 minutes after administration was higher than the ED_{90} value in the cell test as was the case when 30 mg / kg of the aforementioned compound was administered either via the duodenum or orally.

[0181] In order to measure the level [of the drug] in the blood, we prepared a drug administration solution as follows. When the drug was administered intravenously, we prepared a solution made by dissolving 10 mg of the compound being investigated in 0.3 ml of dimethyl acetamide (DMA) and adding PEG400 (0.4 ml) and water (0.3 ml). When the drug was administered via the duodenum or orally, we prepared a solution made by dissolving 30 mg of the compound being investigated in 0.6 ml of DMAO and then adding PEG400 (0.8 ml) and water (0.6 ml). After these solutions had been administered to the rats, blood samples were taken over a period of time, the blood was centrifuged (300 rpm, 10 minutes) and blood plasma was obtained. 20 μ l of the blood plasma was analyzed using HPLC using the following type of column switching method and the concentration [of the drug] in the blood plasma was determined. The conditions for the column switching HPLC were as follows: column 1 used was a TSK Gel G-

2000SW model (manufactured by Tosoh Co., Ltd.) which was 300 mm long and had a diameter of 4.6 mm. An eluate of acetonitrile / 0.5 % phosphoric acid (1 : 9V / V %) was used on this. Column 2 was a YMC A-312ODS model (manufactured by YMC Co. Ltd) which was 150 mm long with a diameter of 6 mm. The eluate used with this column was the same as that used with column 1. However, when the dose was being prepared, the amount of acetonitrile contained therein differed according to the compound being investigated and the proportion ranged from 40 % to 70 %.

[0182]
[Effectiveness of Invention] Compound (I) which is the active ingredient in the drug in the present invention exhibited outstanding and specific HIV protease inhibition activity and also exhibited an inhibition action vis-a-vis virus emission from the HIV infected cells. The compound in the present invention also displayed outstanding oral absorbency and had a high concentration in the blood *in vivo*. Therefore, the present invention is effective as an HIV infection preventive agent, an HIV infection therapeutic agent, an AIDS preventive agent, an AIDS therapeutic agent and / or an HIVprotease inhibitor.

{**Translator's note**: the items which appear at the end of the document are continued from the first page of the document. They have been translated and moved to the beginning of the document for the sake of continuity}